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July 9, 2003

JUL 19 2003

Stephen Kunin
Deputy Commissioner for Patent Examination Policy
UNITED STATES PATENT AND TRADEMARK OFFICE
2121 Crystal Drive
Suite 910
Arlington, VA 22202

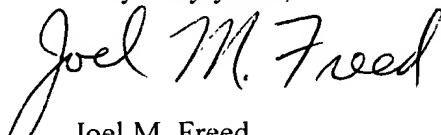
Re: U.S. Serial No. 09/394,745

Dear Stephen:

We represent the Applicants of the above-referenced patent application. Please find enclosed for your attention a Petition to invoke the supervisory authority of the Commissioner under 37 C.F.R. § 1.181, with attached Exhibits A-D. Applicants believe the restriction requirement in this application is improper and amounts to a refusal by the Examiner to examine Applicants' claimed invention. It is our position, supported by precedent, that a refusal by an examiner to examine that which an applicant regards as his invention amounts to a rejection. *Ex parte Holt*, 214 U.S.P.Q. 381, 383 (Bd. Pat. App. 1982); *Appln. of Haas*, 486 F.2d 1053, 1056, 179 U.S.P.Q. 623, 625 (C.C.P.A. 1973).

Please advise us promptly of your decision on the enclosed petition. We invite you to contact us directly should you have any questions regarding the matters set forth in the accompanying papers.

Very truly yours,


Joel M. Freed
David R. Marsh

Attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

JUL 29 2003

Dane K. FISHER *et al.*

Art Unit: 1637

Appln. No.: 09/394,745

Examiner: Young J. KIM

Filed: September 15, 1999

Atty. Docket: 16517.001/38-21(15454)B

For: ***Nucleic Acid Molecules and Other
Molecules Associated with Plants***

Petition under 37 C.F.R. §1.181

Attention: Office of Deputy Commissioner for Patent Examination Policy
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Responsive to the Decision on Petition mailed May 12, 2003, Applicants hereby petition the Commissioner to invoke his supervisory authority and require the Examiner to reopen prosecution and examine the invention claimed by Applicants. It is well-settled law that a restriction requirement may only be issued *between* claims, not within a single claim. *Appln. of Weber*, 580 F.2d 455, 458-459, 198 U.S.P.Q. 328, 332 (C.C.P.A. 1978); *Appln. of Haas*, 580 F.2d 461, 464, 198 U.S.P.Q. 334, 336-337 (C.C.P.A. 1978); *Appln. of Haas*, 486 F.2d 1053, 179 P.2d 1056. Moreover, it is not what the Office regards as the invention that is to be examined; rather, it is what the applicant sets forth as the subject matter sought to be patented that is to be examined.¹ By requiring Applicants to elect a single combination for examination, the Office has improperly required restriction within a claim. In addition, the restriction requirement in this application amounts to a refusal by the Examiner to examine Applicants' claimed invention, and

¹ See *Appln. of Wolfrum*, 486 F.2d 588, 591 ("[u]nder this provision of § 112, the scope of the subject matter is governed not by the examiner's conception of the 'invention' but by that 'which the applicant regards as his invention.' ") 179 P.2d 1056

that amounts to a rejection. *Ex parte Holt*, 214 U.S.P.Q. 381, 383 (Bd. Pat. App. 1982); *Appln. of Haas*, 486 F.2d 1053, 1056, 179 U.S.P.Q. 623, 625 (C.C.P.A. 1973).

On January 10, 2003, Applicants petitioned the Commissioner under 37 C.F.R. § 1.144 to review the improper restriction requirement; that petition was denied. Applicants have also petitioned the Commissioner for reconsideration of that decision; that petition was also denied on May 12, 2003. Therefore, Applicants submit that it is necessary and proper for the Commissioner to invoke his supervisory authority to address the improper refusal to examine the invention claimed and the improper restriction requirement within the claimed invention. This petition is timely-filed within two months of mailing of the Decision on Petition regarding Applicants' Request for Reconsideration of Applicants' Petition under 37 C.F.R. § 1.144.

1. Statement of Facts

Many of the facts in the present petition have already been established in the Petition under 37 C.F.R. § 1.144 filed on January 10, 2003, and in the subsequent communications with the Office. Thus, only the most pertinent facts will be repeated herein.

A. The Invention

On October 10, 2000, Applicants filed a Preliminary Amendment ("Preliminary Amendment") in the present application containing claims 8-11. The invention embodied in claim 8 and its dependent claims (9 and 10) is directed to a microarray comprising a substrate with a surface comprising 10^3 nucleic acid molecules or more where at least 10% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from a group.² See specification at page 59, line 25 through page 62, line 7.

² A copy of the currently pending claims, as presently pending in the application, is attached hereto as Exhibit A. The complete text of claims 8-10, as originally filed in the Preliminary Amendment are also attached hereto as Exhibit B.

B. The Restriction Requirement

In the Office Action mailed December 19, 2000 (“Restriction Requirement”), the Office restricted the application to one of two groups, with group I consisting of claims 8-10 and group II consisting of claim 11. The restriction between groups I and II was subsequently withdrawn and is not among the issues presented herein. More importantly, with respect to the subject of the present petition, the Office relying on the apparent authority of M.P.E.P. § 803.04, asserted that it would pose an “undue burden to perform a search on every combination of 100 nucleic acid molecules selected from a set of 400 molecules”. For that reason the Office declared that Applicants were “required to select one combination for examination” and that examination “will be restricted to only the elected combination.” Restriction Requirement at pages 2-3.

Applicants traversed both restriction requirements, but provisionally elected group I (claims 8-10) and “the first 100 sequences in the Markush group”. Response to Restriction Requirement dated April 17, 2001 (“Response to Restriction Requirement”) at pages 2-3. Further, Applicants responded specifically to the additional restriction requirement imposed within the invention embodied in claims 8-10 by submitting evidence that it would not pose an “undue burden” on the Office. In particular, Applicants argued

It took applicants’ representative less than 10 minutes to set up the BLASTN search. After the BLASTN search was completed, Applicants’ representative spent approximately 2 hours examining and parsing the BLASTN output with the purpose of selecting those sequences which either had no matches to any sequence in the queried database or which fulfilled other criteria. In this case, the Examiner is being asked to examine only 498 [sic – 497] sequences, rather than approximately 3000. Applicants representative submits that even if the Examiner were to search a larger database than the one described above, or use a different search algorithm, the time for running a program is not synonymous with the actual time that an Examiner would have to spend on a search. To further avoid any undue search burden the PTO is encouraged to refer to the preliminary amendment of October 10, 2000 in which applicant [sic] submitted a copy of the BLASTIN output on CD-ROM.

Response to Restriction Requirement at page 2. This argument apparently fell on deaf ears and Applicants were subsequently required by the Office to expressly recite the 100 SEQ ID

Numbers elected for further examination. *See* Office Action mailed May 21, 2001 and Reply to Detailed Action dated July 3, 2001.

Specifically, the Office rejected Applicants' argument on the basis that the Office would follow a standardized sequence searching procedure, stating in pertinent part:

the PTO does not conduct searches in like manner. For each claimed SEQ ID Number, the Office must perform a sequence search, for each SEQ ID Number, on a commercial database . . . , PTO in-house database, and the issued-patent database.

Office Action mailed March 18, 2002 ("First Office Action") at page 2. However, for reasons that will be discussed herein (*see, e.g.*, Sec. 3(d) below), this position is not sustainable.

The First Office Action also appeared to require Applicants to amend claim 8 such that the group of nucleic acid sequences recited by the claim only included the 100 sequences elected for examination. The obtuse language in the First Office Action, *i.e.*, "the examination of SEQ ID Numbers will not go beyond the 100 SEQ ID Numbers" (First Office Action at page 2), was not only confusing and misleading, but outright inaccurate. Even this subset of the original group of sequences submitted in claim 8 was not properly examined. In particular, the examination of claim 8 stopped as soon as one novel sequence, *i.e.*, SEQ ID NO: 5893, was identified. *See* First Office Action at page 10.

If nothing else, the Final Office Action mailed September 11, 2002 ("Final Action") highlighted the Office's inability to properly apply its articulated restriction practice in M.P.E.P. § 803.04 to the claimed invention. More particularly, the Final Action clarified that no amendment to claim 8 had in fact been required. The Final Action states

Applicants are advised that the actual combination of 'one hundred' SEQ ID Numbers was selected by Applicants, and was not required by the Examiner. Applicants were requested to elect a single combination of nucleic acids . . . In other words, Applicants could have elected all of the recited SEQ ID Numbers as the combination to be examined.

Final Action at page 2. This language, as indicated above, contradicts the earlier statement made by the Office in the First Office Action, but also shows that no amendment to claim 8 was required.

More importantly, the language quoted above highlights the inappropriateness of the restriction requirement *within* the invention of claim 8. The positions taken by the Office throughout prosecution demonstrate how convoluted the restriction requirement is when applied to the invention claimed. It was never apparent at any point what an elected combination might be as applied to this invention. That is because the claimed invention can never be defined by a single combination, as the Office would like it to be.

Lastly, however, the Final Action makes clear that the Office, from the beginning of prosecution, made no effort to determine what the invention claimed actually was because the Office was determined to examine a different invention from that claimed by Applicants. Specifically, the Final Action states that

[i]f Applicants are traversing that such a requirement should not have been made, Applicants are referred to MPEP 803.04, example C, wherein it explicitly states that such combination claims would be subject to restriction requirement wherein Applicants will be required to “select one combination for examination.”

Final Action at page 2. MPEP 803.04 is based on the Office’s position that each nucleotide sequence “is presumed to represent an independent and distinct invention”. M.P.E.P. § 803.04. Furthermore, the First Office Action made clear that examination of claim 8 stopped as soon as one novel sequence, *i.e.*, SEQ ID NO: 5893, was identified. In short, the Office had no intention *ever* to examine the invention claimed, but rather elected to examine a single nucleic acid sequence. Regardless of whatever policy the Office may rely on, this type of examination is improper.

C. The Prior Petitions

Applicants have continued to contest the inappropriateness of the restriction requirement imposed within the invention embodied in claim 8 and its dependents. On January 10, 2003, Applicants filed a petition under 37 C.F.R. § 1.144 (“Petition”) requesting the withdrawal of the restriction requirement to select a single combination of nucleotide sequences for examination. In response to the Petition, on February 14, 2003, the Office mailed a decision (“First Decision”) denying Applicants’ Petition. On April 14, 2003, Applicants filed a Request for Reconsideration of Applicants’ Petition under 37 C.F.R. § 1.144 (“Request”), which was subsequently denied by the Office on May 12, 2003, in a second petition decision (“Second Decision”).

Applicants have additionally expressed their position that the demand to select a single combination of nucleotides for examination and the subsequent acts of the Office, however denominated, constitutes a rejection; and that rejection has now been twice made, thereby being ripe for appeal. As such, on June 30, 2003, Applicants filed an Appellant’s Brief directed to the rejection of claims 8-10 by the actions of the Office summarized above. In conjunction with this filing, Applicants also submitted a letter to Stephen Kunin, Deputy Commissioner for Patent Examination Policy (“Letter”), a copy of which is attached hereto as Exhibit C, expressing Applicants’ intentions to proceed with the appeal or, if the Office should refuse to entertain the appeal, to petition for a writ of mandamus to the Federal Circuit. In response to this letter, Applicants’ representatives received a phone call from Robert Barr on July 1, 2003, inviting them to submit the present petition directly to the Office of the Deputy Commissioner for Patent Examination Policy.³

³ To the extent that the Office considers the present petition in a timely and expeditious manner, Applicants intend to withhold proceeding on an appeal to the Board of Patent Appeals and Interferences directed to the refusal to examine the claimed invention. Furthermore, as indicated in the Letter (Exhibit C), Applicants consider the present acts by the Office as an indication that a final decision on the restriction requirement has not been lodged. However, Applicants herein reserve their right to proceed on the appeal should at any time it become apparent that the Office will not give due consideration to Applicants’ present petition. Furthermore, Applicants herein reserve their right to petition for a writ of mandamus to the Federal Circuit, as indicated in the Letter, should it become apparent that the Office will not entertain any appeal on the rejection of claims 8-10 by way of a refusal to examine the claimed invention.

2. Issues Presented in this Petition

The issues in the present Petition under 37 C.F.R. § 1.181 are whether the refusal to examine the invention embodied in claims 8-10 because of alleged undue burden constitutes an improper rejection, and particularly, whether the purported restriction requirement within a single claim (not between claims) and the insistence that the invention as claimed will not be examined constitutes an improper rejection.

3. Argument

(a) Summary of Applicants' Position

Applicants have disclosed and claimed a single invention. Applicants' invention is a microarray that can be modified by its user to select for specific nucleic acid molecules of interest in a given sample. Accordingly, the invention contemplates the ability to include or exclude any nucleic acid molecule comprising any one or more of the nucleic acid sequences that is a member of the group of nucleotide sequences set forth in claim 8. Admittedly, that puts thousands of different combinations of nucleic acid molecules within the scope of claim 8, such is Applicants' invention – not a single combination. From the commencement of prosecution, the Office disregarded Applicants' claimed invention and required that Applicants select *one* combination of nucleic acid molecules for prosecution, ignoring the essence of the invention. In effect, the Office has refused to examine the invention as claimed. This refusal to examine what Applicants rightfully regard as their invention in accordance with 35 U.S.C. § 112, second paragraph, amounts to a rejection. *Ex parte Holt*, 214 U.S.P.Q. 381, 383 (B.P.A.I. 1982); *Appln. of Haas*, 486 F.2d 1053, 1056, 179 U.S.P.Q. 623, 625 (C.C.P.A. 1973).

That the Office purports to find authority in its restriction practice is irrelevant. It is well-settled law that a restriction requirement may only be issued *between* claims, not within a single claim. *Appln. of Weber*, 580 F.2d 455, 458-459, 198 U.S.P.Q. 328, 332 (C.C.P.A. 1978); *Appln. of Haas*, 580 F.2d 461, 464, 198 U.S.P.Q. 334, 336-337 (C.C.P.A. 1978); *Appln. of Haas*, 486

F.2d 1053, 1056. By requiring Applicants to elect a single combination for examination, the Office has improperly required restriction within a claim. No number of divisional or continuation applications directed to different combinations of the thousands of permissible combinations comprehended by the invention as originally claimed could ever amount to the whole of Applicants' invention. And even the full complement of individual applications directed to all those combinations would not effectively constitute the entirety of Applicants' invention, as the examination of each would not be the same as the examination of the integrated whole presented in claims 8-10.

The assertion by the Office that it would pose an undue search burden to perform a search on every combination envisioned by the claimed invention is not a justification for the improper refusal to examine the integrated whole. The Office is obliged to examine Applicants' invention and not some subset it would rather examine.

Applicants ask the Office to take official notice of extensive pleading from the intellectual property community to implement appropriate examination procedures and eschew the current policy that relies on overzealous restriction practice, allegedly justified by the purported "undue burden" to the Office. Applicants submit the "undue burden" asserted by the Office has been imposed on the Office by itself because it clings to archaic search procedures. In any event, as the Court of Customs and Patent Appeals, the predecessor of the Court of Appeals for the Federal Circuit, and the tribunal presently charged with judicial supervision of the Office, has declared, "in drawing priorities between the Commissioner as administrator and the applicant as beneficiary of his statutory rights, we conclude that the statutory rights are paramount."

Appln. of Weber, 580 F.2d 455, 458-459.

The Office can examine claims 8-10 if it would but do what the biotechnology industry and academia (*see* sec. 3(d) below) routinely do when it comes to searching. Its refusal to do so is the problem here, not Applicants' claims.

(b) The Claimed Invention Was Never Examined by the Office

Claim 8 and its dependents were improperly subjected to restriction requirement, even under the guidelines set forth in M.P.E.P. § 803.04. *See* Restriction Requirement at page 3. This restriction requirement was based on a misconstruction of the nature of Applicants' claimed invention and, most importantly, it effectively denied Applicants their statutory right to have what they regard as the invention examined. 35 U.S.C. § 112, second paragraph. *See also* *Appln. of Haas*:

we note that the board did attempt to ‘go behind the bare words because of the possibility that a rejection in fact has been mislabeled as a withdrawal (or objection). . . That a de facto rejection had been made without statutory basis was also not considered. The withdrawal from any further consideration was instead classified as a ‘refusal. . . to act on claims’ in keeping with a restriction requirement and deemed a purely administrative matter.

Appln. of Haas, 486 F.2d 1053, 1056; *Appln. of Weber*:

[a]n applicant is given, by the statute, the right to claim his invention with the limitations he regards as necessary to circumscribe that invention, with the proviso that the application comply with the requirements of s 112.

Appln. of Weber, 580 F.2d 455, 458; and *Appln. of Wolfrum*:

[u]nder this provision of § 112, the scope of the subject matter is governed not by the examiner’s conception of the ‘invention’ but by that ‘which the applicant regards as his invention.’

Appln. of Wolfrum, 486 F.2d 588, 591, 179 U.S.P.Q. 620, 622 (C.C.P.A. 1973).

Applicants characterize the invention embodied in claim 8 as a microarray having a substrate with a surface comprising 10^3 nucleic acid molecules or more where at least 10% of the nucleic acid molecules (1) are different and (2) at least about 250 nucleotide residues and (3) complementary to a molecule having a sequence selected from a group. Petition at page 7. The invention includes thousands of collections and combinations of nucleic acid molecules for the skilled practitioner to select from when determining how best to screen a sample for the detection of a desired nucleic acid molecule or molecules. *See* Petition at pages 7-9. However, that invention was never examined by the Office.

Instead of recognizing that the invention claimed by Applicants is a microarray that has the ability to be modified by the user to select for a specific nucleic acid molecule or molecules of interest, the Office immediately divided the invention into subparts. Specifically, the Office required that Applicants elect a *single* combination and insisted that examination would be limited to this, and only this, combination. Restriction Requirement at page 3. Essentially, what the Office did was require that Applicants subject their invention to piecemeal examination, destroying the whole of the invention itself. Even if Applicants were able to bear the financial burden associated with filing and prosecuting thousands of applications,⁴ each one directed to a different combination that may be selected by the user of Applicants' claimed microarray, the end result would fall far short of accomplishing examination of the *invention*. This is because the invention as claimed allows for the user to select which nucleic acid molecule or molecules to include or exclude from the substrate of the microarray. Piecemeal examination disregards the selectivity by the user which is embodied in Applicants' invention. More importantly piecemeal examination is in effect no examination of the whole invention.

If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification.

Appln. of Weber, 580 F.2d 455, 458. The Office admits as much. Although in the First Decision the Office asserted that the restriction requirement applied to claim 8 and its dependents did not rewrite the claimed invention, in this same paper the Office states that

Applicants may claim as many combinations as they wish. So long as the claimed combinations include SEQ ID NO: 5893, they are free of the prior art and no further search would be required to examine such claims.

⁴ For example, at a minimum, if Applicants were to file 497 applications, each one directed to a microarray which must include a specific SEQ ID NO, as the Office has done here (*see sec. 3(d) and footnote 5 infra*), the cost to Applicants would be \$372,750 in initial filing fees for the Office alone. Furthermore, even this expenditure would not allow Applicants' to have examined what they regard as the invention.

First Decision at page 2. But all the combinations within Applicants' claims do not require the inclusion of SEQ ID NO: 5893, and the Office is not free to limit Applicants' invention to combinations which do include SEQ ID NO 5893.

If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. . . If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits.

Appln. of Weber, 580 F.2d 455, 458. Yet that is precisely what the Office has admitted it has done. The Second Decision further confirmed that the invention examined by the Office was not the same invention claimed by Applicants. The Second Decision states:

First Applicants argue that the examiner, by forcing applicants to elect a single combination of sequences for examination, has narrowed the scope of the claims.
This is correct, and that was the purpose of the restriction requirement.

Second Decision at page 2 (emphasis added). Essentially, the Office has confirmed in these admissions that the invention claimed by Applicants was never examined, and was refused examination. Rather, the invention examined by the Office would require the user of Applicants' microarray to always include SEQ ID NO: 5893 on the microarray substrate, even if this sequence posed no interest to a user of the microarray.

Applicants here are not claiming SEQ ID NO: 5893, either permanently embedded on a microarray substrate or in isolation. Applicants' invention is a microarray in which no single variation is characteristic of the claimed microarray, rather it is the ability to modify, substitute and select different collections or combinations of recited nucleic acid molecules, including the ability to choose precisely which molecules to include or exclude from those listed in the recited group, that creates the essence of Applicants' invention. Applicants' invention is not a fixed microarray, but rather the invention provides the ability to vary the contents of a microarray within the parameters set forth in the claim. And as such, Applicants' claimed invention was never examined by the Office and this amounted to a rejection of claims 8-10.

It is apparent that the Office is intent on avoiding examination of Applicants' claimed invention and instead is seeking to find an easy way out by limiting the invention to an uncharacteristic trait (i.e., a single molecule) that guarantees novelty. However, it is the Office's obligation to examine for novelty what Applicants present as their invention, not to artificially inject novelty into a claim by treating the claim as if it were limited in a way the Office would like it to be limited.

(c) The Restriction Requirement Amounts to a Rejection of the Claimed Invention

As previously mentioned, it is well-settled law that a restriction requirement may only be issued *between* claims, not within a claim directed to a *single* invention. *Appln. of Weber*, 580 F.2d 455, 458-459; *Appln. of Haas*, 580 F.2d 461, 464; *Appln. of Haas*, 486 F.2d 1053, 1056. The Office may not divide up a single invention for piecemeal examination.

Claim 8 and its dependents embrace a single invention. The restriction requirement divided that invention into single combinations which did not constitute the more generally claimed microarray. The Office relies on M.P.E.P. § 803.04 to classify each nucleic acid molecule within Applicants' invention as an "independent and distinct" invention, however, this classification fails to take into account the whole of the invention claimed. Applicants are not claiming nucleic acid molecules in isolation, nor are Applicants claiming a combination of molecules embedded on a substrate of a microarray which are characterized by the presence of one particular nucleic acid molecule (*i.e.*, SEQ ID NO 5893). Rather, the disclosed and claimed invention is a microarray that allows one to efficiently analyze large amounts of nucleotide sequences for a target sequence or a fragment of that sequence, and to vary the parameters of that search based on available nucleic acid molecules comprising a selected assortment of nucleic acid sequences.

The Office may not rely on an articulated policy to arbitrarily apply restriction practice where it is not proper. *Ex parte Holt*, 214 U.S.P.Q. 381, 384. By imposing restriction within the

invention encompassed by claim 8 and its dependents, the Office removed from consideration the selectivity crux of Applicants' invention. In addition, because the restriction requirement divided the invention claimed, no matter how many applications are filed directed to particular combinations of the claimed microarray, Applicants are precluded from presenting their integrated invention in another application. *Cf. Appln. of Hengehold*, n.11, 440 F.2d 1395, 1404, 169 U.S.P.Q. 473, 480, 58 C.C.P.A. 1099, 1110 (C.C.P.A. 1971). The restriction requirement did more than just divide Applicants' invention, it destroyed the invention as a whole.

Furthermore, the overzealous use of restriction practice, particularly as applied to biotechnology inventions, effectively denies Applicants any recourse in the courts. The Office here has demonstrated its willingness to apply § 803.04 indiscriminately, without regard to the invention actually claimed. In doing so, the Office may gain what it might perceive as a benefit in refusing to examine the invention claimed by Applicants, but the Office does so only by simultaneously purporting to prevent an appeal of the issue to a higher authority (*i.e.*, by calling its refusal to examine the claimed invention, which amounts to a rejection, a restriction). It is unequivocal that the Office refused to examine the invention claimed by Applicants and attempted to divide the microarray into pieces that could under no circumstances amount to the whole of the invention, including the selectivity feature. Thus, under the guise of restriction practice, the Office has in fact rejected Applicants' invention.

At the same time, because restriction practice is a petitionable matter, no recourse may be left for Applicants to immediately appeal the *de facto* rejection of the claimed invention. The Office is thus able to continue, unfettered, a policy of rejecting Applicants' invention through restriction practice, in clear contradiction to precedential holdings, while usurping the jurisdiction of the Board of Patent Appeals and Interferences and the Federal Circuit to review the policy of § 803.04 and the Office's application thereof.

In the present case, the restriction requirement amounted to a rejection of the claimed invention. It is indisputable that the restriction requirement destroyed the whole of the invention

and the examination of its parts can never amount to examination of the whole. Moreover, it is well-established that restriction practice is only permissible between claims directed to different inventions and not within a single claim or group of claims directed to a single invention. As such, the restriction requirement imposed on Applicants' microarray amounted to a rejection of that invention.

(d) There Is No Undue Burden on the Office to Examine the Claimed Invention

The Office wishes to sustain the restriction requirement of claims 8-10 because it would allegedly present an "undue burden to perform a search on every combination of 100 nucleic acid molecules selected from a set of 400 molecules." Restriction Requirement at page 2. This position cannot prevail.

The rationale above is, first, inaccurate. Although Applicants acknowledge that thousands upon thousands of different collections and combinations are envisioned in the claimed microarray, Applicants submit that the Office should direct its attention to determining the novelty of all of the individual nucleic acid sequences set forth in the group of sequences of claim 8.⁵ That is because if they are all novel, all combinations contemplated within the scope of the claimed invention would be novel. If any one of them is found not novel, Applicants would be required to reexamine the parameters of the claimed invention and present either arguments or amendments to comply with the requirements for patentability, as they would in any other invention examined by the Office.

To that end, Applicants here have already provided assistance to the Office by submitting a CD-ROM that includes the results of the search performed by Applicants prior to adding claims 8-10 to the Application. Applicants explained that

⁵ The Second Decision argues that "[b]ecause the Office does not have the resources for such an undertaking, USPTO policy is to require applicants to elect a single combination for examination, as set forth in MPEP 803.04." Second Decision at page 2. That requirement is inconsistent with governing authority, as previously discussed.

[b]ased on analysis of the BLASTN output the original set of 2921 sequences was reduced by selecting only those sequences which were greater than 400 nucleotides and (a) had no matches to any public sequence in the queried database, or (b) matched for the top hit (best E value) . . . to a public sequence in the queried database in only a single high scoring pair . . . of less than 100 nucleotides where the match had an expectation (E value) greater than 1E⁻³.

Preliminary Amendment at page 15. Although the First Decision appears to make jest of Applicants' submission,⁶ the reality is that the results of Applicants' search greatly reduces the amount of time and effort required by the Office to determine the novelty of these nucleic acid sequences. In particular, the First Office Action states that “[f]or each claimed SEQ ID Number, the Office must perform a sequence search, for each SEQ ID Number, on a commercial database (which included multiple databases), PTO in-house database, and the issued patent database.” First Office Action at page 2. Under this rationale, Applicants have already certified their results for one-third of the work the Office asserts it would need to do.

Furthermore, Applicants have submitted evidence that a search of 497 nucleic acid sequences would not pose an *undue* burden on the Office, but rather a *reasonable* one. In response to the Restriction Requirement, Applicants pointed out that

It took applicants' representative less than 10 minutes to set up the BLASTN search. After the BLASTN search was completed, Applicants' representative spent approximately 2 hours examining and parsing the BLASTN output with the purpose of selecting those sequences which either had no matches to any sequence in the queried database or which fulfilled other criteria. In this case, the Examiner is being asked to examine only 498 [sic – 497] sequences, rather than approximately 3000. Applicants representative submits that even if the Examiner were to search a larger database than the one described above, or use a different search algorithm, the time for running a program is not synonymous with the actual time that an Examiner would have to spend on a search. To further avoid any undue search burden the PTO is encouraged to refer to the preliminary amendment of October 10, 2000 in which applicant [sic] submitted a copy of the BLASTIN output on CD-ROM.

⁶ The First Decision states “Applicants magnanimously offer to assist in searching the prior art for the sequences listed in the claims, and point out that the USPTO is considering using prior art searches performed by commercial search authorities in the future.” First Decision at page 2.

Response to Restriction Requirement at page 2. To date, the Office has submitted no evidence to contradict Applicants assessment of the *actual* time and effort required by the Office to perform a similar search.

In any event, the burden issue is a red herring. For reasons already explained, the Office is obligated to examine Applicants' claimed invention. Restriction between claims may be proper, but restriction within claims is not.

As a general proposition, an applicant has a right to have Each claim examined on the merits. If an applicant submits a number of claims, it may well be that pursuant to a proper restriction requirement, those claims will be dispersed to a number of applications. . . If, however, a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim.

Appln. of Weber, 580 F.2d 455, 458. And a refusal to examine the invention based on such a restriction constitutes an improper rejection.

We hold, therefore, that the Board of Appeals has jurisdiction under 35 U.S. C. § § 7 and 134 to review an adverse decision of an examiner when that decision, although designated a ‘withdrawal’ of a claim from further consideration, is in fact a rejection of that claim on the ground that it encompasses independent and distinct inventions.

Appln. of Haas, 486 F.2d 1053, 1056.

Yet, the Office chooses to disregard both the law and Applicants’ prior search submitted on CD-ROM. The evidence offered by Applicants supports the position that a search of the nucleic acid sequences listed in claim 8 would not pose an “undue burden”. The only position the Office advances in response is that “[a]t the present time, all prior art searches for U.S. patent applications are performed ‘in house.’ ” First Decision at page 2. However, this position is not sustainable. As Applicants have previously pointed out,

[f]or example, the Office currently provides for an applicant to submit prior art references and certify that he has made or caused to be made a careful and thorough search of the prior art in situations where a Petition to Make Special under 37 C.F.R. § 1.102 has been granted. See MPEP § 708.02. Moreover, the

Office has acknowledged that ‘[a]pplicants are generally in the best position to identify the most pertinent prior art related to their invention(s).’

Request at page 8. The merits of considering a search by applicants is also contemplated by the Office in the 21st Century Strategic Plan.⁷

When the evidence is considered as a whole, it becomes clear that the only undue burden on the Office regarding the examination of multiple nucleic acid sequences is the burden the Office imposes on itself. Several solutions have been offered on multiple occasions to ease the search and examination burden of the Office. On every occasion, the Office resists these changes. For example, because the issued-patent database is available to interested members of the community, it is not beyond reason to suggest that applicants could perform this portion of the search and certify the results, as well as submit their own searches of publicly available databases. The Office may even easily develop guidelines and requirements that these searches must meet before the Office will consider the results. This solution was offered by several members of the patent community at the Public Hearings on Patenting of Nucleic Acid Sequences (“Hearings”) on April 16 and April 23, 1996 (attached hereto as Exhibit D). Abuse of this proposed procedure is presently guarded against by an applicant’s duty of candor under 37 C.F.R. § 1.56 and by publication of patent applications after 18 months.

Numerous other solutions have been offered by the patent community, for example, in the Hearings, in response to the 21st Century Strategic Plan, and at user conferences.⁸ Several examples from the Hearings include (1) charging additional fees for the examination of inventions that include sequences in excess of a prescribed amount; (2) eliminating excess

⁷ See also *Four-Tracks Patent Examination Process*, Productivity, Pendency 2 at page 9 (“Many times, applicants possess the expertise to recognize and identify the most pertinent prior art patents and publications related to their invention(s). Review of the ISSR will result in applicant identification of significant patentability issues related to novelty and obviousness before an examiner even begins, thus enabling examiners to better spend their time on the analysis of patentability that is critical to patent quality.”)

⁸ See, for example, the quarterly Biotechnology/Chemical/Pharmaceutical Customer Partnership Conferences, designed and developed to be a forum to share ideas, experiences and insights between individual users and the Office.

sequences from databases used by the Office to avoid redundancy; (3) outsourcing to private, specialized search firms; (4) developing software and/or searching methods for the Office and examiner training; (5) using BLAST searches, such as the one performed by Applicants, and other filtering systems to narrow the number of sequences requiring further search and examination; and (6) two-part examination. Furthermore, adoption of any of one or more of these suggestions would be consummate in scope with the goals expressed in the 21st Century Strategic Plan.

All of these options were originally offered or suggested in the Hearings conducted in 1996. The Office could have taken steps to implement them then and, because of the advancement of technology, could even more easily and cheaply implement them now. However, in 1996, the Office seized on the ability to use a resource already available to them – restriction practice – in spite of warnings from the patent community that this practice was already overzealously applied. Moreover, when the Office publicized its “new” policy regarding the Examination of Patent Applications Containing Nucleotide Sequences (1192 O.G. 68, October 17, 1996), the Office stated that several of the other possible solutions proposed in the Hearings would be examined.⁹ To date, however, the Office still clings to this archaic “quick fix” while simultaneously claiming it would be an “*undue* burden” to search more than one sequence. This burden is unquestionably self-imposed.

In the present case, Applicants have demonstrated that the current restriction practice, embodied in M.P.E.P. § 803.04, applied to applications containing nucleic acid and amino acid sequences is improperly imposed to restrict within a single invention and to avoid examination of the invention claimed. Moreover, the Office cannot sustain its position that examination of more than one sequence in an application poses an undue burden. Rather, it is the Office itself that is

⁹ Since this publication in the Official Gazette, the Office has not publicized any changes, proposed changes, studies, hearings, statistics, data, etc., that would lead those in the industry to believe that any progressive steps have been taken by the Office to modernize the policy expressed in M.P.E.P. § 803.04 or to explore any of the alternatives proposed in 1192 O.G. 68.

guilty of imposing an undue burden on Applicants by taking away their opportunity to have what they regard as their invention examined in accordance with the law.

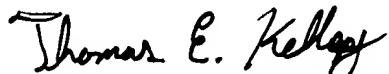
Conclusion

In view of the foregoing, Applicants specifically petition the Commissioner to invoke his supervisory authority and require the Examiner to reopen prosecution, remove the improper restriction requirement and examine the invention claimed by Applicants.

Applicants request that the \$130.00 fee for filing a Petition be charged to Deposit Account No. 50-2387, referencing matter number 16517.001/15454B.

In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned. Applicants do not believe any additional fees are due in conjunction with this filing. However, if any fees under 37 C.F.R. §§ 1.16 or 1.17 are required in the present application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Deposit Account No. 50-2387, referencing matter number 16517.001/15454B. A duplicate copy of this Petition is attached.

Respectfully submitted,


Thomas E. Kelley (Reg. No. 29, 938)
by Holly Logue Prutz (Reg. No. 47,755)
David R. Marsh (Reg. No. 41,408)

Date: July 9, 2003



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202.942.5000 telephone
202.942.5999 facsimile

Exhibit A

8. A microarray comprising a substrate with a surface comprising 10^3 nucleic acid molecules or more where at least 10% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from the group consisting of SEQ ID NO: 5776, SEQ ID NO: 5781, SEQ ID NO: 5782, SEQ ID NO: 5783, SEQ ID NO: 5785, SEQ ID NO: 5787, SEQ ID NO: 5800, SEQ ID NO: 5804, SEQ ID NO: 5815, SEQ ID NO: 5818, SEQ ID NO: 5821, SEQ ID NO: 5823, SEQ ID NO: 5828, SEQ ID NO: 5830, SEQ ID NO: 5832, SEQ ID NO: 5836, SEQ ID NO: 5838, SEQ ID NO: 5840, SEQ ID NO: 5845, SEQ ID NO: 5849, SEQ ID NO: 5850, SEQ ID NO: 5851, SEQ ID NO: 5856, SEQ ID NO: 5859, SEQ ID NO: 5863, SEQ ID NO: 5868, SEQ ID NO: 5871, SEQ ID NO: 5874, SEQ ID NO: 5875, SEQ ID NO: 5877, SEQ ID NO: 5893, SEQ ID NO: 5896, SEQ ID NO: 5901, SEQ ID NO: 5908, SEQ ID NO: 5909, SEQ ID NO: 5920, SEQ ID NO: 5922, SEQ ID NO: 5926, SEQ ID NO: 5928, SEQ ID NO: 5929, SEQ ID NO: 5931, SEQ ID NO: 5936, SEQ ID NO: 5937, SEQ ID NO: 5939, SEQ ID NO: 5941, SEQ ID NO: 5944, SEQ ID NO: 5945, SEQ ID NO: 5950, SEQ ID NO: 5955, SEQ ID NO: 5960, SEQ ID NO: 5961, SEQ ID NO: 5963, SEQ ID NO: 5964, SEQ ID NO: 5968, SEQ ID NO: 5973, SEQ ID NO: 5974, SEQ ID NO: 5991, SEQ ID NO: 5994, SEQ ID NO: 5999, SEQ ID NO: 6000, SEQ ID NO: 6001, SEQ ID NO: 6005, SEQ ID NO: 6006, SEQ ID NO: 6007, SEQ ID NO: 6011, SEQ ID NO: 6017, SEQ ID NO: 6018, SEQ ID NO: 6022, SEQ ID NO: 6023, SEQ ID NO: 6026, SEQ ID NO: 6030, SEQ ID NO: 6033, SEQ ID NO: 6042, SEQ ID NO: 6046, SEQ ID NO: 6059, SEQ ID NO: 6063, SEQ ID NO: 6065, SEQ ID NO: 6066, SEQ ID NO: 6089, SEQ ID NO: 6091, SEQ ID NO: 6098, SEQ ID NO: 6106, SEQ ID NO: 6107, SEQ ID NO: 6110, SEQ ID NO: 6117, SEQ ID NO: 6121, SEQ ID NO: 6124, SEQ ID NO: 6131, SEQ ID NO: 6137, SEQ ID NO: 6141, SEQ ID NO: 6144, SEQ ID NO: 6145, SEQ ID NO: 6147, SEQ ID NO: 6154, SEQ ID NO: 6167, SEQ ID NO: 6168, SEQ ID NO: 6170, SEQ ID NO: 6173, SEQ ID NO: 6178, and SEQ ID NO: 6181.

9. A microarray according to claim 8 where at least 75% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from said group.

10. A microarray according to claim 8 where at least 95% of the nucleic acid molecules are comprised of different sequences and at least about 250 nucleotide residues and complementary to a molecule comprising a sequence selected from said group.

Exhibit B

Claims as originally filed in the Preliminary Amendment of October 10, 2000

8. A microarray having a substrate with a surface comprising 10^3 nucleic acid molecules or more where at least 10% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a molecule having a sequence selected from the group consisting of SEQ ID NO: 5776 and SEQ ID NO: 5781 and SEQ ID NO: 5782 and SEQ ID NO: 5783 and SEQ ID NO: 5786 and SEQ ID NO: 5787 and SEQ ID NO: 5800 and SEQ ID NO: 5815 and SEQ ID NO: 5818 and SEQ ID NO: 5821 and SEQ ID NO: 5823 and SEQ ID NO: 5828 and SEQ ID NO: 5830 and SEQ ID NO: 5836 and SEQ ID NO: 5838 and SEQ ID NO: 5840 and SEQ ID NO: 5845 and SEQ ID NO: 5849 and SEQ ID NO: 5850 and SEQ ID NO: 5851 and SEQ ID NO: 5859 and SEQ ID NO: 5863 and SEQ ID NO: 5868 and SEQ ID NO: 5874 and SEQ ID NO: 5875 and SEQ ID NO: 5877 and SEQ ID NO: 5893 and SEQ ID NO: 5896 and SEQ ID NO: 5901 and SEQ ID NO: 5909 and SEQ ID NO: 5922 and SEQ ID NO: 5926 and SEQ ID NO: 5928 and SEQ ID NO: 5931 and SEQ ID NO: 5936 and SEQ ID NO: 5937 and SEQ ID NO: 5939 and SEQ ID NO: 5941 and SEQ ID NO: 5950 and SEQ ID NO: 5955 and SEQ ID NO: 5956 and SEQ ID NO: 5963 and SEQ ID NO: 5973 and SEQ ID NO: 5974 and SEQ ID NO: 5991 and SEQ ID NO: 5994 and SEQ ID NO: 5999 and SEQ ID NO: 6000 and SEQ ID NO: 6001 and SEQ ID NO: 6005 and SEQ ID NO: 6006 and SEQ ID NO: 6007 and SEQ ID NO: 6011 and SEQ ID NO: 6017 and SEQ ID NO: 6022 and SEQ ID NO: 6023 and SEQ ID NO: 6030 and SEQ ID NO: 6033 and SEQ ID NO: 6059 and SEQ ID NO: 6065 and SEQ ID NO: 6089 and SEQ ID NO: 6091 and SEQ ID NO: 6106 and SEQ ID NO: 6107 and SEQ ID NO: 6110 and SEQ ID NO: 6117 and SEQ ID NO: 6121 and SEQ ID NO: 6124 and SEQ ID NO: 6137 and SEQ ID NO: 6154 and SEQ ID NO: 6167 and SEQ ID NO: 6168 and SEQ ID NO: 6170 and SEQ ID NO: 6173 and SEQ ID NO: 6178 and SEQ ID NO: 6181 and SEQ ID NO: 6188 and SEQ ID NO: 6195 and SEQ ID NO: 6196 and SEQ ID NO: 6205 and SEQ ID NO: 6211 and SEQ ID NO: 6212 and SEQ ID NO: 6214 and SEQ ID NO: 6234 and SEQ ID NO: 6241 and SEQ ID NO: 6245 and SEQ ID NO: 6251 and SEQ ID NO: 6256 and SEQ ID NO: 6261 and SEQ ID NO: 6270 and SEQ ID NO: 6272 and SEQ ID NO:

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9. A microarray according to claim 8 where at least 75% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a molecule having a sequence selected from said group.

10. A microarray according to claim 8 where at least 95% of the nucleic acid molecules are different and at least about 250 nucleotide residues and complementary to a molecule having a sequence selected from said group.

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June 30, 2003

Stephen Kunin
Deputy Commissioner for Patent Examination Policy
UNITED STATES PATENT AND TRADEMARK OFFICE
2121 Crystal Drive
Suite 910
Arlington, VA 22202

Hand-Delivered

Re: U.S. Serial No. 09/394,745

Dear Stephen:

We represent the Applicants of the above-referenced patent application. Enclosed for your immediate attention is a Notice of Appeal with attached Exhibit A, and an Appeal Brief for the above-referenced application. Applicants believe the restriction requirement in this application is improper and amounts to a refusal by the Examiner to examine Applicants' claimed invention. It is our position, supported by precedent, that a refusal by an examiner to examine that which an applicant regards as his invention amounts to a rejection. *Ex parte Holt*, 214 U.S.P.Q. 381, 383 (Bd. Pat. App. 1982); *Appln. of Haas*, 486 F.2d 1053, 1056, 179 U.S.P.Q. 623, 625 (C.C.P.A. 1973).

Applicants previously presented their grievances pertaining to the restriction requirement issued by the Examiner in the above-referenced application to the Office via a Petition under 37 C.F.R. § 1.144, which was subsequently denied in a decision issued by the Office. Applicants then proceeded with a Request for Reconsideration of Applicants' Petition under 37 C.F.R. § 1.144. That Request was also denied in a decision issued by the Office. Therefore, Applicants believe the refusal to examine the claimed invention by the Office amounts to a rejection, and that rejection has now been twice made. As such, this issue is ripe for appeal. Accordingly, Applicants have appealed and request that the appeal, addressing the refusal to examine the invention claimed, be consolidated with the appeal already pending in this application.

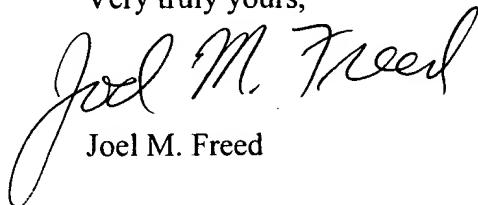
ARNOLD & PORTER

Stephen Kunin
June 30, 2003
Page 2

Please immediately advise us whether the Office will entertain this present appeal, or whether the Office will refuse to do so. (We recognize that the Office ordinarily treats matters pertaining to restriction as petitionable and not appealable.) If the Office does the latter, or if we do not receive a response from you by July 7, 2003, please be advised that Applicants intend to petition the Federal Circuit for a Writ of Mandamus regarding the issues presented in the accompanying appeal brief.

A copy of this letter, the appeal brief, and accompanying documents are being hand-carried to the Office of the Commissioner of Patents and to the Board of Patent Appeals and Interferences in support of Applicants' position.

Very truly yours,



Joel M. Freed

Enclosures

COPY

HEARING AND REQUEST FOR COMMENTS ON ISSUES RELATING
TO PATENT PROTECTION FOR NUCLEIC ACID SEQUENCES

University of California, San Diego

International Center

April 16, 1996

Reported By: TERESA BURT, CSR NO. 8607

PANEL MEMBERS:

Bruce A. Lehman
Stephen G. Kunin
Edward R. Kazenske
Lawrence J. Goffney
Nancy J. Linck

1 MR. LEHMAN: My name is Bruce Lehman. I'm the
2 assistant secretary of commerce and commissioner of patents
3 and trademarks.

4 And joining me today in this hearing are
5 Lawrence J. Goffney, acting deputy district secretary of
6 commerce and acting deputy commissioner of patents and
7 trademarks.

8 To my immediate right, Edward Kazenske, deputy
9 assistant commissioner for patents.

10 To my left, Stephen Kunin, deputy assistant
11 commissioner for patent, policy and projects.

12 Over here on my far right, Nancy Linck, the
13 solicitor, the chief lawyer of the Patent and Trademark
14 Office.

15 I'd like to first thank the University of
16 California at San Diego for providing this facility for us.
17 This is the second time we've been out here in this campus.

18 This is a hearing to receive public comment on
19 a serious problem currently facing the Patent and Trademark
20 Office related to patent protection for nucleic acid
21 sequences.

22 The public was invited to comment on this
23 issue in a notice published on March 12th, 1996, in Volume
24 61, No. 49 of the Federal Register.

25 For over a decade, the Patent and Trademark
26 Office has been examining and granting patents to claims

COPY

27 receiving nucleic acid sequences. The scientific and
28 technological advances have permitted the rapid
4
1 identification of large numbers of genes or gene fragments.
2 The ease of utilizing automated techniques for sequencing
3 nucleic acid fragments has resulted in the filing of a
4 growing, although still relatively small number, of patent
5 applications, each of which claim thousands of nucleic acid
6 sequences.

7 Statistics reveal that the number of these
8 applications is growing, and based on the number of
9 organisms in genes still to be discovered, such growth will
10 continue for the near future.

11 In fiscal year 1991, the scientific and
12 technical information center of our Patent and Trademark
13 Office searched about 4,000 sequences. In fiscal year '95,
14 they searched about 22,000 sequences. Currently we have
15 over 200,000 sequences claimed and at least 70 patent
16 applications awaiting search and examination.

17 Our estimates show that the search of 100
18 sequences requires about 15 hours of computer time. But
19 the evaluation of the search results for those 100
20 sequences requires about 65 hours of examiner time. The
21 PTO currently has two massively parallel processor
22 computers and could run the searches in about two years,
23 when the computers are running 24 hours a day, seven days a
24 week.

25 To examine this relatively small number of
26 patent applications only with respect to the prior art,
27 however, would require only 9- -- would require over 90
28 senior-level staff years. Thus, in order to accommodate --
5
1 in order to process these applications, the entire staff of
2 the Biotechnology Patent Examining Group 1800 would have to
3 work for more than nine months exclusively on these
4 applications.

5 These applications present a challenge to us
6 at the PTO, and we need help and suggestions on how we can
7 address the problem. The United States is a leader in the
8 rapidly growing field of biotechnology, which is a growth
9 industry important to the economic health of this country.

10 The PTO has taken a very active role in

11 working with its customers to try to simplify policies and
12 procedures in ways that encourage and promote the growth of
13 this industry.

14 We are committed to improving the
15 responsiveness of the PTO to its customers and to more
16 effectively address the needs of industry. We must find
17 ways to search and examine the pending applications and
18 provide these applicants with appropriate protection -- and
19 I emphasize the word appropriate patent protection -- for
20 the inventions without creating an imbalance in the
21 appropriation of the resources within and among the
22 technologies and the patent-examining groups.

23 These policies established must permit the
24 timely and thorough examination of all applications which
25 require the same resources for completion.

26 We are currently working in partnership with
27 the applicants of these applications in order to explore
28 innovative mechanisms to accomplish the required work in
1 processing them. We appreciate the time each of you has
2 taken to attend this hearing -- all of you in the audience
3 today -- and provide us with input into the solutions to
4 this problem.

5 A transcript of this hearing will be prepared
6 and will be made available for purchase by the public
7 approximately 10 days after this hearing. Copies of the
8 transcript will also be available for purchase directly
9 from the stenographer. The name of the stenographer
10 service today is Peterson & Associates, and their telephone
11 number is area code (619) 260-1069. That's (619) 260-1069,
12 Peterson & Associates.

13 We have received 10 written comments and seven
14 requests to appear orally at this hearing. Any persons who
15 wish to speak and who have not previously informed us of
16 their desire are encouraged to add their names to the list
17 located on the table at the rear of this room.

18 In order to permit all persons requesting to
19 appear orally, including those persons signing up today to
20 present testimony, we would request each speaker to limit
21 their presentation to 15 minutes. Those persons who wish

22 to provide additional comments should submit their comments
23 in writing to us no later than April 23rd.

24 The speakers have been listed, and I think we
25 have a list of them back there, don't we?

26 They've been listed in the order in which the
27 requests were received by us. You may also pick up at the
28 table of the rear of the room copies of the Official
1 Gazette publication of the notice of these hearings and
2 request for comments on issues related to patent protection
3 for nucleic acid sequences.

4 When you present your comments, we would
5 appreciate it if you would please give your name and
6 address and tell us whether these comments are your own or
7 whether they are those of a law firm or company that you
8 represent or whether you represent an organization and are
9 presenting comments on their behalf.

10 Speakers are requested to limit their remarks
11 to the questions presented in the Federal Register
12 publication of March 12th, 1996. And I am told that the
13 first person who is here to testify before us -- where
14 is -- oh, right there -- to testify before us this morning
15 is Alice Martin.

16 So, Ms. Martin, would you please come forward.
17 MS. MARTIN: Commissioner, ladies and
18 gentlemen, my name is Alice O. Martin. I represent the law
19 firm of Brinks, Hofer, Gilson & Lione in Chicago.

20 My address there is the NBC towers. I also
21 believe I am speaking consistent with the position of
22 B.I.O., of which our firm is a member.

23 As attorneys for the biotechnology industry,
24 we applaud the cry from the patent office for help in
25 solving what we consider a very common problem. We
26 appreciate that the examiners are hacking their way through
27 this jungle of nucleotide and amino acid sequence databases
28 and that they face a seemingly unmanageable task and,
1 indeed, as the commissioner mentioned, the jungle is
2 growing even as we speak.

3 Now, some facts affecting this problem are the
4 database -- databases that exist were not specifically
5 designed for the use of obtaining prior art for obviousness

6 rejections but rather they were designed to accumulate and
7 expand on all information on all sequences that are known.

8 The tools for the search algorithms to hack
9 through this jungle were not specifically designed to find
10 prior art for obviousness rejections, but rather they were
11 designed to quantify and describe similarities, sometimes
12 based on an evolutionary model. And many of them are
13 designed to ferret out even distant evolutionary
14 relationships.

15 Another fact addressing this problem is that
16 examiners are currently, as I understand it, not provided
17 with maps or search strategies with which to find their way
18 through this database jungle. This means that they can
19 take false paths, hit dead ends, waste valuable time and
20 become frustrated.

21 Furthermore, the subjective, somewhat
22 unpredictable paths that are basically unreproducible cause
23 uncertainty among applicants and certainly down the road
24 will cause problems in litigation in the courts.

25 Now, how can we make manageable, yet legally
26 sound, solutions to this problem? I suggest we tame the
27 jungle and provide maps through which we could move through
28 the jungle. Now, the tools or the search algorithms used
1 will to some extent depend on the choice of maps.

2 How can we tame the jungle? We're not aware
3 of any legal requirement that the patent office has to do
4 an exhaustive, brute-force search of everything that exists
5 in the current databases. So let's prune the jungle.
6 Let's not search all databases just because they exist,
7 particularly when many of them are repetitive.

8 Perhaps your meeting with experts, as I think
9 has already begun, to explain the construction of the
10 different databases would be helpful so that either you can
11 pick the best database for overall patent searches or pick
12 the best for certain sets of claims. Claims to CD&As may
13 not be using the same database as claims to ESTs, for
14 example. And there are specialized databases that have
15 been developed, for example, by the NIH group for these
16 specialized searches. Perhaps working with these groups

17 already in the field will be helpful.

18 Now, a more extreme suggestion that could be
19 necessary is to plan an entirely new jungle.

20 MR. LEHMAN: Can I ask a question?

21 MS. MARTIN: Certainly.

22 MR. LEHMAN: You said that the NIH has
23 developed these specialized databases for the searches, but
24 the NIH has withdrawn their patent applications. Are you
25 talking about databases they developed for other
purposes or databases --

27 MS. MARTIN: That is my understanding. And
28 I'm not up on the latest but I certainly --

1 MR. LEHMAN: -- they developed for other
2 purposes for their own research purposes?

3 MS. MARTIN: I have read that they were
4 working on specialized databases, and I thought it might be
5 worth exploring, at least whether they have them available
6 or not, what methods they have used to develop those might
7 be very helpful.

8 As I said, a more extreme solution would be to
9 completely plan a new jungle. In this case we would take
10 the old databases and create a new database specifically
11 designed for the purpose of finding prior art upon which to
12 base obviousness rejections.

13 This way perhaps a grouping in the database
14 could be such that you don't have to keep redoing the same
15 kinds of searches over and over, and I'll say a little bit
16 later about the maps that could be used to perhaps organize
17 this database.

18 We also then in the new database could
19 organize it to correspond to different types of claims that
20 are traditionally sent in by applicants. Also it was
21 mentioned, I believe at the April 4th presentation, that
22 there's a problem in determining what is, quote, prior art
23 because of the difficulty in determining what dates various
24 sequences are entered. That information is in the database
25 but is evidently difficult to retrieve, so art can be
26 looked at but really isn't prior art in the current
methods.

28 A new database may also help the problem

11
1 evidently of finding extension numbers and then trying to
2 look in the references that are cited and identify which
3 sequence is really referred to in a particular reference.

4 And finally, one of the reasons I think the
5 patent office gave for using its present databases is that
6 there are references that are retrieved along with the
7 sequences.

8 That may not be something that needs to be
9 done for each sequence and, again, can be considered in a
10 new database.

11 I think everyone agrees that redundant
12 sequences should be removed, and this would be solved
13 either by pruning the databases or developing a new one.
14 Not everyone agrees that sequences should be trimmed first
15 before a search of areas that can give hits that, as some
16 of the developers of the search algorithms say, are of
17 dubious biological significance. And here again it might
18 be helpful to reevaluate the tools that are being used for
19 searches.

20 My understanding is that the PTO has selected
21 a search algorithm because of increased sensitivity. This
22 is puzzling to us because for increased sensitivity, you
23 are picking up more distantly related sequences, when for
24 obviousness rejection, what we really have to focus on is
25 structurally similar sequences. The more distant the
26 relationships, the more likely there are to be structural
27 dissimilarities, making it more difficult to prove
28 obviousness because, number one, the structures are very
12
1 different and, number two, to find art that would suggest
2 or motivate all of the different changes between that
3 distant-claimed and the period-claimed sequence would be
4 very, very rare. So it seems to me that may be defeating
5 the purpose.

6 The patent office search goals appear to be
7 somewhat different from those we use in the scientific
8 community, and I realize that many of the examiners
9 themselves were established scientists and may have to
10 remove their scientific hat and focus not on the biological
11 relationships but what is structurally similar in terms of

12 the legal sense. And here again I have a seminar from
13 technical experts who have developed the different
14 algorithms. Could be very, very helpful.

15 Also, remember that any of these algorithms
16 will find matches because they're really just looking at
17 the sequences as letters and basically searching through to
18 find a probabilistic model that says this sequence is more
19 similar than would be expected by chance. So in and of
20 itself, there is usually no legal or biological
21 significance.

22 And finally, I suggest we develop maps or
23 search strategies rather than jumping into the jungle first
24 and emerging overburdened and overwhelmed with lots of
25 sequences. We need a strategy because searches in the
26 mechanical arts, if you find an application that has a
27 carburetor and a machine, you don't generally look at all
28 the art in the world that has a carburetor.

1 ¹³
2 Similarly in the chemical arts, if you find a
3 composition that has a benzene ring, you don't usually look
3 at all compositions that have a benzene ring.

4 One option is to use key words first before
5 going into a strategy of searching the database. Key words
6 can include species, library, protein or function as
7 related in the claims and the specification. I think
8 considering the claim as a whole, as the courts and the
9 board of appeal have instructed us, may suggest that some
10 sequences don't even have to be searched.

11 We could group sequences, and the applicants
12 here should be helpful in this regard in terms of length,
13 core chemical structure, again to relate to the chemical
14 practice art. If we do these maps, this will provide focus
15 using legal standards that already exist. There's nothing
16 new, I think, in the obviousness of DNA sequences.

17 As you all know, this will be less open to
18 criticism and less open to challenges to validity of the
19 patents than using something such as "Let's look at the
20 first 45 best hits that we get out of the search." That
21 seems to me very arbitrary and I think will open the patent
22 up to much criticism in the future.

23 Plus, by using that kind of ab priori and

24 arbitrary criterium, you may have too many sequences
25 examined for some and too little for others. As we saw in
26 the U.S. Supreme Court decision in Deere, there are two
27 criteria that must establish a prima facia case of
28 obviousness. One, is the claim structure different. And
1 two, are the differences suggested by the art.

2 Both the courts and the board have said DNA is
3 a chemical. Proteins are chemicals, so we must follow the
4 chemical practice, which is the same as iterated in Deere:
5 is the composition structurally similar? And if so,
6 similarity alone will not be a bar unless there are
7 secondary references motivating those changes.

8 For example, a nucleotide change in two
9 positions must have some reference or some motivation in
10 the art to make those particular differences. As we see
11 it, the existence of these massive databases pose a big
12 risk for hindsight and obviousness to try creeping into
13 obviousness rejections. Looking at the time the invention
14 was made, add a database that exists in the world, the
15 inventor is going to be faced with infinite number of
16 possibilities, and it would be unpredictable to merge or to
17 change sequences without some motivation in the art. So we
18 ask that the examiners take caution in selecting these
19 merely by hindsight.

20 Some other things that might be kept in mind
21 in planning our sequences searches are that the courts have
22 already said that defining a sequence and a method of
23 making it will not support an obviousness rejection. One
24 species will not necessarily make obvious a similar
25 sequence in a second species.

26 Here our big problem, I think, boils down to
27 what is structural similarity in terms of DNA and amino
28 acid sequences that can be applied then to the chemical
1 practice standards. We need to decide what is a structural
2 similarity to focus the search rather than getting all
3 sequences that may have some limited degree of similarity.
4 In other words, why look for all sequences because they are
5 somewhat similar if you're not able going to be able to use
6 them in an obvious rejection anyway.

7 Dealing with some of the smaller sequences
8 that we've mentioned that are presented in large numbers, a
9 portion of the sequence is not likely to make a larger
10 sequence obvious because there is no way of predicting that
11 larger sequence, and the courts are certainly going in that
12 direction. If you have a larger sequence, why look for
13 small fragments when there is no teaching of boundaries of
14 the fragment.

15 I think here, too, that applicants may have to
16 take a role in being more second specific in some terms
17 that are now fairly loosely defined such as homologues,
18 analogues, mutants, variants and fragments. These are not
19 mutually exclusive terms. They need to be defined.

20 Now, I know none of us like a piecemeal
21 prosecution. However, there may have to be some
22 negotiation on a 112 section first before a search strategy
23 is planned.

24 In summary, rather than trying to speed up
25 previous ways to do these searches, particularly before
26 encountering these large numbers or large size sequences,
27 we recommend that we reevaluate whether we shouldn't tame
28 the jungle by finding more suitable databases or groups of
1 16
1 databases for the legal search and by developing maps based
2 on obvious criteria already known to the courts and the
3 board so that we can focus the search and not waste
4 valuable time looking at dead ends. Thank you.

5 MR. LEHMAN: Thank you, Ms. Martin.

6 Are there any questions from other members of
7 the panel?

8 Thank you very much.

9 Next I'd like to call on John Burke.

10 MR. BURKE: Good morning. My name is
11 John Burke. I'm here from Maas Parr Computer Corporation.
12 Thank you for having us. I'm going to offer a more
13 technical presentation that won't have much legalities in
14 it.

15 Maas Parr is a database processing company and
16 in support of bioinformatics of a particular --

17 THE REPORTER: I need you to speak up a little
18 bit more. Okay?

19 MR. BURKE: Okay.

20 Maas Parr Computer is a computer database
21 processing company.

22 MR. LEHMAN: Could maybe put this closer to
23 your mouth. Okay?

24 MR. BURKE: Okay. Thank you.

25 And we also do bioinformatics. We are a
26 complete computer system with fast processing as well as
27 the infrastructure that's required by central processing.

28 Our internal communication is 28 megabytes per second, and
1 more importantly we have audio capabilities which are

17

2 needed at the U.S. PTO. We have up to 240 megabytes
3 transferred from the disk to the computer core which will
4 be very important doing the number of searches that you
5 have to perform.

6 The advantages to U.S. PTO are a quick access
7 to the database, very flexible access, which is very
8 important of your current model of operation. Because you
9 have many independent investigators working on different
10 patent applications, it's not possible to order the
11 database searches. And with many architectures, it's
12 necessary to preload the database. And therefore to
13 optimize your search time, you would have to perform the
14 searches in a certain order on certain databases. And with
15 our systems, this isn't necessary.

16 As well, the entire range of bioinformatics
17 applications are accelerated, not just the database
18 searching. As you mentioned, one of the problems is the
19 bottleneck in investigator time, and so to accommodate
20 this, we are parallelizing the entire range of applications
21 that support the interpretation of search results.

22 We're a very flexible architecture and very
23 easy to develop one. We have over 260 installations with
24 other 100 computers in universities where research is being
25 performed. Over 26 installations are specific to audio
26 informatics, so there's a very good basis for this.

27 A result of such a large basis is continual
28 application development and development of tools for the
18
1 processing of results.

2 The result of having so many bioinformatics
3 applications running is that investigator review time can
4 be restricted. Not only do we have the database searching
5 tools but we have many database processing tools which is
6 very important to removing the redundancies inherent in
7 biological databases and also to reduce the number of
8 results returned and save the amount of time that an
9 investigator might have to spend going through and
10 examining results manually.

11 In addition to the bioinformatics tools and
12 computer system, Maas Parr Computer Corporation has
13 professional services with experience in designing
14 automated DNA processing for hybrid screening. That would
15 mean that the reviewer time is saved both in setting up the
16 searches but also in the interpretation of the results
17 because much of the interpretation can be automated, and we
18 do have experience in this field.

19 In addition we have educational services on
20 the high level, even on the high level on how to use
21 bioinformatics applications on providing search strategies
22 and also to the lower levels of maintaining hardware,
23 programing, language and such. Additionally, we have
24 worldwide, 24-hour customer service support.

25 Now I wanted to provide some level of
26 specificity in dealing with the problems mentioned in the
27 announcement for this hearing, but there is limited time,
28 so I would just like to talk about one application that's
1 19
2 very suitable for today, and that is the clustering
3 methodology that we have employed for biological sequences.

4 One of the big problems with biological
5 databases, as mentioned before, is that there are a large
6 number of redundancies, so therefore clustering refers to
7 the attempt to reduce the bulkiness and the cumbrousness
8 of the database while at the same time preserving all the
information content.

9 One possible model for the use of a clustering
10 methodology is the database processing which is done at the
11 systems support level at the U.S. PTO. This would not be
12 done by the investigator but the infrastructures and the
13 support mechanisms available to the investigator. A

14 database would be clustered, processed into another
15 database, then having the redundancies removed and making
16 them a smaller overall size.

17 The benefits are faster search time because
18 there are less entries, but more importantly the results of
19 such a database search would be much more easy to interpret
20 because there are less redundancies and less multiple hits.

21 Another model for use in clustering is by the
22 investigator himself or herself. Clustering can be done at
23 any level of stringency that the investigator decides is
24 necessary, and one possibility is doing prior art searches
25 on multiple databases and then obtaining the results which
26 would be very large and probably very redundant with much
27 repetition.

28 The search results can be clustered to produce
29 20
1 processed results which will have the redundancies removed,
2 and it will be much easier to go through. Thus, you save
3 time in the interpretation of the results and eye strain on
4 the investigator having to look at multiple hits of the
5 same thing.

6 A very big problem in searching databases,
7 especially EST, is that there are many ESTs for one gene,
8 and really you only need the information of the gene
9 itself. A clustering methodology would allow you to have
10 one hit per one gene. That will greatly reduce the size of
11 the databases. That will greatly reduce the amount of time
12 that an investigator needs to interpret the results of his
13 or her search.

14 The third instance where Maas Parr feels that
15 clustering will be of use is tackling the problem of mass
16 injuries, where instead of the single sequence, you might
17 have hundreds or even thousands of sequences in the one
18 application. The idea here would be for the investigator
19 to run his or her own clustering of the data set that's
20 provided of the patent application that's provided.

21 The clustering would be done at the level of
22 similarity that they choose, and the output will be a
23 processed submission which will contain the original
24 sequence data, but more importantly the sequence data will

25 be put into work groups that are similar in pontiff levels,
26 a similarity that's chosen by the investigator.

27 This saves a lot of time because instead of
28 viewing the patent application as thousands of individual
21 1 sequences, he or she can view the application as a whole in
2 its work groups and a first-level organization has been
3 provided which will save the amount of time needed to
4 process the application and the amount of searching that
5 you'll have to do.

6 That's only one of the applications available
7 for database processing from -- in the Maas Parr system,
8 but we felt it was the most relevant to discuss today
9 because it attacks the problem of mass submission. It
10 addresses the problem of the investigator time needed to
11 analyze the results. It even allows one to work on the
12 database level to try to clean up databases to remove
13 redundancies, to try to improve some of the -- some of
14 the -- not flaws but particularities of the U.S. PTO
15 situation.

16 So in conclusion, Maas Parr is striving to
17 reduce investigator time as well as provide fast, rapid
18 bioinformatics tools in parallel.

19 MR. LEHMAN: We're using your system right
20 now. Is this the first time some of these -- that we've
21 heard some of these suggestions, or have you been giving
22 them to our --

23 MR. BURKE: This is the first time that you've
24 heard about clustering, yes. Right now U.S. PTO is using
25 the Maas Parr to do rapid database searching and such.

26 The clustering tools are rather new, but they
27 are working currently. And they're meant for large-scale
28 uses in database and also small-scale use an individual
22 1 investigator would do.

2 MR. LEHMAN: When you deal with the PTO, do
3 you deal with the informations systems people primarily
4 or --

5 MR. BURKE: Primarily, I believe that we deal
6 with the information systems.

7 MR. LEHMAN: -- as opposed to the examining
8 core directly?

9 MR. BURKE: Yes.
10 MR. LEHMAN: Are there any other questions?
11 MR. KUNIN: You began to mention a little bit
12 about the process of post processing in addition to the two
13 styles of clustering. The first speaker spoke in terms of
14 setting up a process of post processing which might include
15 the formation of an expert system which would kind of help
16 analyze the search results from the perspective of the law,
17 that is, to collect the information not only from the
18 standpoint of identity but also enough structural
19 similarity and relationships that might suggest how some of
20 that -- some of the results might be combined for
21 obviousness purposes. Do you have any comments from
22 -- for Maas Parr on the post-processing solution?

23 MR. BURKE: The post-processing solution, we
24 have some experience, and we have implemented similar
25 systems in the commercial companies. It refers to
26 automatic screening of sequences. I believe that she was
27 speaking of a -- of a set methodology before -- sort of --
28 I believe she was referring to guidelines for the
1 investigators in doing their searches.

23

2 I think that would be very useful, and an
3 automated schema can be put in place to save time. I
4 personally feel that the investigator should have a
5 latitude to perform any kind of search they want, though.
6 I think such things should be a guideline only and not a
7 straitjacket, but such a thing is very possible and is a
8 very good idea, yes.

9 MR. LEHMAN: You know, you've heard the
10 suggestions of the previous witness and made some of your
11 own, and you also heard my little opening comments. And my
12 opening comments suggest quite a large gap between the
13 resources under our present methodology which would be
14 required to examine these applications and what would be
15 reasonable, given our present fee structure and resources.

16 Can you give me some kind of judgment on your
17 part as to what -- how much of this gap would be reduced in
18 your view by the proposals that you've offered?

19 MR. BURKE: As far as the specific amount --

20 MR. LEHMAN: It doesn't help us very much
21 to -- to -- to -- to chop it away 10 percent of a problem
22 that is -- is totally debilitating. We need to chop away
23 99 percent of it.

24 MR. BURKE: Yes. It's not just going to be
25 buying more hardware, although that will be necessary,
26 considering how much work you have ahead of you but also
27 the methodologies that you'll need like this clustering.

28 As far as a reduction of database size, I
29 24
1 don't know. It won't be on the level of 50 percent.
2 However, on the other end by the individual investigator,
3 it could save quite a bit of time in mass applications
4 because there's bound to be a lot of redundancy, and why do
5 a thousand searches when you can do a hundred. I think you
6 will need to buy more hardware. You will need to
7 modernize, but more importantly, you'll have to start --
8 you'll have to keep up with the latest technology and
9 automated processing and clustering and other such tools
10 that can help you do more than just database searching in
11 prior art investigations.

12 So you asked me for a specific number or a
13 guess as to the amount of time that can be saved. I
14 don't know that I could do that, but on the top of my head,
15 I can think about it, but I do know that it will -- you
16 have to -- just by buying -- buying more of them will not
17 solve the problem but employing smarter systems of the kind
18 that I'm talking about today will -- will provide the
19 solution.

20 MR. LEHMAN: Thank you very much.

21 MR. BURKE: Thank you.

22 MR. LEHMAN: Next I'd like to call
23 Suzanne Biggs.

24 MS. BIGGS: Good morning, commissioner,
25 gentlemen and lady. I'm Suzanne Biggs. I'm with the La
26 Jolla office of the law firm of Lyon & Lyon, 4250 Executive
27 Square, Suite 660, La Jolla, California 92037.

28 This testimony and comments that I'm giving
29 25
1 today reflect my own opinions and should not be considered
2 as representing the position or opinion of Lyon & Lyon or
3 of any of its clients. They reflect some of my experiences

4 as a practitioner in this area.

5 Lyon & Lyon is a law firm specializing in
6 intellectual property law. I work primarily advising
7 clients in patent matters, particularly in the areas of
8 biochemistry, chemistry and biotechnology. I've been
9 specializing in biotechnology and biochemistry for about
10 the last six or seven years.

11 We understand the concerns of the Patent and
12 Trademark Office, that they want to issue good patents that
13 are directed to novel, unobvious, useful subject matter
14 that will stand up to challenge in the courts. That's what
15 we want to obtain for our clients as well.

16 We also understand their concern with regard
17 to the burden of examining certain applications. However,
18 I'm not so sure that proposing differential fees is the
19 right way to go about it. These proposed differential fees
20 raise three questions to my mind.

21 Is it appropriate to base fees on the
22 technology type? Is it appropriate to base fees on the
23 estimated difficulty of search by some sort of objective
24 criteria? Is it appropriate to revise fees in a piecemeal
25 manner when the PTO finds that a particular group of
26 applications appear to be more difficult to examine than
27 the norm? I believe that the answer to all three questions
28 should be no.

26

1 With regard to the suggestion that fees be
2 based on technology type, we believe it would be unfair to
3 pick out biotechnology applications to have higher fees
4 just based on the fact that they're biotechnology.

5 Typically, biotechnology companies are small
6 companies. They're money sensitive. Patents are critical
7 to their continued existence, to their continued ability to
8 raise funds, to their ability to get their products to
9 market. Biotechnology companies typically are one area
10 where we seem to be extremely good at competing with the
11 other companies in the world. In fact, so many corporate
12 deals are being done with foreign companies, they must
13 think that our biotech people are very innovative.

14 Differential fees that are much higher would

15 discourage patent filings. It probably would not stop them
16 from filing the ones they see as clear winners, but some of
17 the ones that may be enabling technology, it would
18 encourage them keeping things such as trade secrets. It
19 would decrease the amount of information that enriches the
20 area in general.

21 Also, another thing to consider is not all
22 biotechnology applications are large and unwieldy to
23 examine. Very few contain thousands of sequences that have
24 to be searched. It appears that one of the things that
25 have really sparked these hearings are a small number of
26 applications that seem to have caused particular problems
27 and problems that may not be representative of all
28 biotechnology applications.

27
1 Also, another point to consider is large and
2 unwieldy applications, meaning those that are hard to
3 examine, are not limited to biotechnology. Other
4 technology areas have applications that prove difficult to
5 examine and take a large amount of examiner time.
6 Applications in the computer and software area and other
7 high-tech areas and as time goes on with new technologies,
8 I think a variety of them will have problems that way,
9 particularly in their early stages.

10 As the industry progresses and matures,
11 biotechnology applications will become more focused and,
12 indeed, many of them are becoming more focused now. People
13 are directing them to more specific solutions to problems.
14 And I think this will continue to happen as the art
15 matures.

16 Therefore, it is believed that it would be bad
17 precedent to increase fees for one type of application in
18 general such as biotechnology when there seem to be
19 problems examining them or whenever you get a new
20 technology type which doesn't really have established
21 guidelines for examination.

22 Other fee considerations are -- many -- even
23 focused biotechnology applications often have a large
24 number of claims and as such they are already paying higher
25 filing fees than many applications in the, for example,
26 mechanical arts, where claim numbers of several hundred are

27 unusual.

28 Also, as the industry matures -- and even now
28
1 while it's sort of in its adolescence and companies are
2 looking for corporate partners to help fund clinical trials
3 and the like -- many of these applications are losing their
4 small-entity status, and as that increasingly happens, that
5 will increase the fees the patent office gets, but it will
6 also increase the fee burden on the companies.

7 I have a few comments to make about sequences
8 and numbers. There's -- we've all heard some comments that
9 possibly fees be based on the number of sequences in the
10 application. And one thing, as the rules stand now,
11 anytime a sequence of four or more amino acids -- as long
12 as there are no D amino acids or 10 or more nucleotides are
13 listed in the application, they must be put forth in the
14 sequence listing.

15 In many applications, the majority of these
16 sequences, one, are not claimed, two, need not be searched
17 to determine patentability of what is claimed. Many of
18 these sequences are present in the application to satisfy
19 the requirements of Section 112: how to make, how to use,
20 best mode. There are things like best primers. There are
21 things like plasmid liter sequences, things that the
22 applicant does not expect to get patent coverage on.
23 Often, they will be things that if anyone would be entitled
24 to patent coverage, it would be a company that, say,
25 provides primers, plasmids and the like. So we believe
26 that it would not be appropriate to base these fees on the
27 number of sequences.

28 We can charge higher fees just because there
29
1 are a large number of sequences in the application, where
2 these sequences need not be searched in order to determine
3 whether a patent should issue on the claim subject matter.

4 In fact, complying with the sequence listing
5 requirements can be fairly burdensome in some of these
6 applications just because of the number. We can understand
7 the importance because you all, however you decide to
8 determine your database, need to have all these sequences
9 that are known in it where appropriate, but for determining

10 whether a particular applicant is entitled to a patent,
11 they're just plain not germane.

12 I've heard several suggestions for easing the
13 alleged problem of searching sequences. At present, it
14 seems to be limited to a relatively small number as
15 compared to all biotechnology-type applications but very
16 large applications. And perhaps guidelines can be made to
17 determine what a common focus should be when multiple,
18 large numbers of sequences are being claimed, but that's
19 something for those who are more involved with those sorts
20 of applications to deal with.

21 There's also been some suggestion of
22 applicants making a prefiling search and putting forth some
23 sort of certificate. There is a provision now in petitions
24 to make special, where applicants are requested to put
25 forth -- one of the grounds is a prefiling search and
26 various representations.

27 In view of the sorts of representations and
28 the uncertainties of how those would be construed in a
30
1 later proceeding, I see in my own experience very little
2 use of those provisions. And with respect to a prefiling
3 certificate of some sort of search by applicants, I see
4 some problems.

5 Those problems would be: and how do you
6 standardize what has been searched? What databases do you
7 have to say this search was done within a certain number of
8 days before filing? Also, in determination of guidelines,
9 how close does something have to be before you have to note
10 it in your certification?

11 The other issue that I can see is a problem
12 is: Who would make the certification data that a
13 particular search that fits certain criteria is made?
14 Would it be the attorney? If it's the attorney, that would
15 further increase costs for the small clients because it
16 would require a fair amount of attorney time to review the
17 search and the protocol.

18 If it's a nonattorney, how would we know what
19 the quality was of the people doing such a search, that
20 they really understand the databases, they understood the
21 criteria? I can't -- these are just issues to consider in

22 going forward with any sort of the suggested changes, and I
23 thank you for your time and your consideration.

24 MR. LEHMAN: Thank you.

25 Are there any questions?

26 MS. LINCK: I have one question.

27 You mentioned that we may not search all the
28 sequences disclosed in the application, but what happens
31
1 then when the claims are amended to claim one of the
2 sequences that wasn't searched initially but was disclosed?

3 MS. BIGGS: You would have searched at that
4 time the sorts of sequences. I was particularly commenting
5 on, for example, you have an application where you've
6 isolated a new protein from a source. You have cloned the
7 protein. Many of the sequences that are involved in the
8 cloning are probes, primers, things like that that under
9 these regulations in the 37 CFR 2nd, 821 and so forth will
10 have to be listed. However, these are things often that
11 are either known sequence or they're things that you just
12 are not claiming. They are just not related to what is
13 being claimed. They're not related to the proteins,
14 sequence of the protein that are being claimed. They're
15 not related to the CDNA.

16 MR. LEHMAN: But we would have to identify --
17 these are in the prior art already, which is what the
18 search accomplishes. Would you offer an admission in the
19 application that these are prior art sequences?

20 MS. BIGGS: Well, if we're not claiming the
21 sequence, many times we will say where the sequence comes
22 from, that they come from a particular provider of liters
23 that one puts in a mass mix or they're just things that we
24 don't claim. Of course, if we later claim them, they would
25 have been searched, but just as one pays if you start
26 out with 20 claims and you add another 40, you pay for
27 them. If one were to amend one claim to add an additional
28 50 sequences that the Patent and Trademark Office could do
32
1 if they were to base a fee on the number of sequences that
2 were claimed as opposed to presently the application they'd
3 deal with that, but many of those sequences don't need to
4 be searched.

5 MR. LEHMAN: So would you support an increase
6 in fees if in fact an amendment would be made that required
7 additional searches to cover the additional costs of the
8 search?

9 MS. BIGGS: Right. Now, first of all, I don't
10 support increased fees for biotechnology applications. I
11 would have to see some sort of proposed regulation. I
12 think in general where they're focused, it's without a full
13 review of all sorts of applications that may be difficult
14 to search. I don't think it's fair to pick out one area of
15 technology as having -- that may be easier to quantify. It
16 would be like in pharmaceuticals if you have a group that
17 claims more than 1,000 compounds, you have to pay extra.
18 And some of those, I'm sure, must be very difficult to
19 search appropriately because of -- even with the
20 restriction practice as it is now.

21 MS. LINCK: But if there was a method for
22 adjusting fees to make it fair across the board, have the
23 fees more aligned with the actual costs to the office,
24 would that be something you would consider?

25 MS. BIGGS: I'd have to see a concrete
26 proposal I think.

27 MS. LINCK: Thank you.

28 MS. BIGGS: Thank you.

1 MR. LEHMAN: Thank you very much.

2 I'd next like to ask Richard Klobuchar,
3 please.

4 MR. KLOBUCHAR: Good morning, commissioner,
5 members of the trade office and members of the public. My
6 name is Dr. Richard Klobuchar. I'm currently vice
7 president of the corporation of Science Applications
8 International Corporation. SAIC is headquartered here in
9 San Diego. My office is at 200 North Glebe Road in
10 Arlington. I'm currently also the chief scientist for
11 SAIC's Systems Engineering and Technical Assistance support
12 contract for the Patent and Trademark Office and currently
13 co-principal investigator for a pending distributed
14 supercomputer project with ARPA and the PTO which is
15 referred as to the Metacomputage Project. These comments
16 represent the comments of my corporation.

17 SAIC is an employee-owned, diversified,
18 high-technology research and development services company
19 focusing on information systems, telecommunications,
20 security, transportation and health. Our 22,000 employees
21 are organized across autonomous sectors and transform
22 emerging information technologies into customer-focused
23 solutions for literally thousands of government and
24 commercial customers. Under the competitively awarded
25 System Engineering and Technical Assistance contract for
26 the United States Patent and Trademark Office (USPTO),
27 we have been performing such technology infusion tasks
28 since June of 1993.

34

1 Since September 21st of 1995, SAIC, as the
2 PTO-SETA contractor, has been supporting the USPTO in the
3 selection of hardware, software and approaches to
4 facilitate their examination of biotechnology patent
5 applications. Efforts to date have focused on the analysis
6 of requirements and has resulted in a Preliminary Molecular
7 Sequence Searching Systems Requirements Analysis document
8 dated December 19th, 1995.

9 We anticipate continued efforts for the USPTO
10 through a new Task Order entitled "Automated Support for
11 Biotechnology Patent Examination." Under this Task Order,
12 the SAIC PTO-SETA staff will provide technical and
13 analytical support to enhance USPTO capabilities for
14 automated biosequence searching in support of PTO
15 examiners.

16 On the 15th of March 1996, SAIC's Laboratory
17 Sensors and Automation Division, located here in San Diego,
18 entered into a contractual relationship with Incyte
19 Pharmaceuticals, Inc., for the development of a
20 next-generation robotic system in support of Incyte's DNA
21 sequencing operations.

22 On the 18th of March, SAIC notified the USPTO
23 that via the Internet, we had discovered the work being
24 performed by SAIC's Laboratory Sensors and Automation
25 Division in San Diego. In our OCI notification letter, we
26 described the work being performed by SAIC's Laboratory
27 Sensors and Automation Division. We went on to explain

28 that the role of that laboratory is strictly in the area of
29 35
1 robotic enhancement for the Incyte laboratory equipment
2 and, therefore, we felt that no Organizational Conflict of
3 Interest (OCI) existed. Nonetheless, concerns have been
4 raised by the USPTO that there is the potential for a
5 perceived OCI by the public, especially for those
6 corporations who compete with Incyte in the filing of
7 biotechnology patent applications.

As a result of these concerns, we agreed to two actions; one, to develop an OCI Mitigation Plan and, two, to make a public statement, this statement, regarding our activities. The OCI Mitigation Plan was delivered to the USPTO on the 2nd of April. That plan fully identifies and addresses all possibilities for a perceived OCI in task areas pertaining to support for biotechnology patent examination. Our plan establishes Organizational Controls in order to isolate the SETA contract from all the other contracts being performed by SAIC, both physically and operationally. Further, the plan establishes an Information Control System consisting of Physical, Data, and Administrative controls in order to protect sensitive information from public disclosure. And, all SETA personnel assigned to any biotechnology-related task will receive special, targeted OCI training in order to reinforce the execution of this Mitigation Plan. We believe that this Mitigation Plan addresses USPTO OCI concerns, ensures the confidentiality of USPTO information, and has removed any remaining OCI obstacles for the continuing PTO-SETA support. Thank you.

12 suggestions that I won't mention today that we could not
13 come to agreement on, but we certainly appreciate the
14 opportunity to come and talk to you again.

15 MR. LEHMAN: This reflects the Bio Industry
16 Trade Associates Patent Committee?

17 MS. LUTHER: Right.

18 First of all, I think we have to look back to
19 October 1994 and applaud you on the progress made. We are
20 also here to propose future goals and even some specific
21 suggestions on how to accomplish them.

22 Biotechnology comes of age: 11 major.

23 biotechnology products qualified for marketing in the last
24 year alone. The list of problems solved by biotechnology
25 drugs grows longer.

26 First of all, recombinant insulin, a protein
27 manufactured for diabetics; recombinant human growth
28 hormones to help children grow to normal size, recombinant
37
1 hepatitis B to protect people from liver destruction;
2 recombinant t-PA to stop heart attacks in their tracks and
3 return people to productive lives in days, as opposed to
4 weeks; recombinant Factor VIII to stop the crippling
5 bleeding in hemophiliacs -- a pure drug which alleviates
6 obtaining Factor VIII from the commercial blood supply,
7 which formerly resulted in many bleeders getting hepatitis,
8 then AIDS; Epivir for AIDS; Doxil for Kaposi's sarcoma;
9 Vitasert for CMV retinitis.

10 To fund this tremendous research effort,
11 companies have needed the promise of getting a patent to
12 protect their efforts and give them enough money to pay
13 back their investors. The companies themselves only seek
14 to patent isolated and purified DNA and proteins, as they
15 exist in our laboratories after the hard work of our
16 scientific research teams. Patents did not cover DNA in
17 your own body. Patents are only wielded against
18 competitors which try to profit from our inventions.

19 Many more biotech products are in the works
20 and in the news. The early drug pipeline has literally of
21 hundreds of drugs in Phase I and Phase II studies.

22 Many new products and services are used in the

23 emerging biotech market arena. It is highly computerized.
24 As you heard from our gentleman at Maas Parr, now
25 sequencing machines can prepare sequences for easy loading
26 into computers. Computers programs have been designed to
27 compare sequences and permit the scientist sitting at the
28 computer terminal to make realistic predictions about the
1 structure and function of recombinant protein.
38

2 Computer-modeled drugs are going into clinical testing.

3 Companies interested in leveraging
4 biotechnology expertise can turn to a number of genomics
5 companies, including my employer Incyte Pharmaceuticals, to
6 out-source their biotechnology discover. We genomics
7 companies provide new therapeutic proteins, diagnostic
8 probes, human receptor targets for drugs. Breast cancer
9 and obesity genes are examples of Incyte's competitors'
10 successful collaborations. But enough of our success,
11 let's look at the PTO accomplishments in detail.

12 In October of 1994, you took quite a beating
13 over the utility issue. At that time, you insisted that
14 you wanted to give us quality patents we could take to the
15 bank. And you instituted changes. You issued guidelines
16 and legal rationale for changes. The PTO followed up to
17 assure that these changes would be implemented by the
18 examiners. You drafted explicit examples which showed
19 examiners how to reject claims but also how to allow claims
20 when we met the appropriate standard of proof. You
21 implemented quality control and achieved value on the
22 utility front.

23 Another great accomplishment that is just
24 beginning, the patent office has been training a new crop
25 of examiners to propose allowable claim language on the
26 first action. This revolutionary change, if sustained by
27 the office, could save biotechnology companies millions in
28 patent attorney fees, and these millions will be used to
39
1 further research. This would eliminate unnecessary
2 narrowing of claims. It would eliminate prolonged file
3 history battles. It would eliminate some of the problems
4 we have encountered in celebrated cases such as Genentech
5 versus Novo Nordisk.

6 A third accomplishment, you also appointed

7 biotech practice specialists, who monitored the performance
8 of individual examiners and specifically retrained
9 examiners. Though I haven't had to resort to them yet,
10 they being there holds great promise in helping assure
11 quality and fairness throughout the biotech examining
12 group.

13 And two weeks ago you demonstrated, for the
14 first time in my memory, your sequence searching
15 techniques. You have developed a fine system as the art
16 and science have evolved. You are being complimented on
17 bringing your sequence source problem to the attention of
18 the public so we as customers can help.

19 Future issues. Sequence searching. This is a
20 really big problem. We hope to continue to work with you
21 to build a fair and efficient searching technique. These
22 are difficult and complicated computer techniques and
23 bioinformatic techniques. They can help make your job a
24 lot more efficient. We would like to see you craft an
25 internal quality standard or set of standards for
26 searching, much as you did with utility. I will provide
27 some detailed suggestions on that in a moment.

28 Another big issue that you need to address is
1 the scope of claims for patents with DNA and amino acid
2 sequences. It varies considerably. Some examiners present
3 precise sequences. Others will allow broader scope. In
4 fact, it is relatively easy to substitute DNA codons, as 1
5 to 6 codons specify each amino acid. Similarly,
6 conservative substitutions of amino acids have been known
7 for more than a decade; one amino acid with another
8 comparable one, so that there is no change in structure or
9 function. This state of recombinant technology art is such
10 we must change the human sequence for more efficient
11 cloning in bacteria.

12 There are computer programs now which will
13 convert an efficient human gene into an efficient E. coli
14 gene. If the examiner limits the claim to a particular DNA
15 sequence, competitors could avoid such a narrow claim. If
16 we are to have a patent we can go to the bank on, we need
17 adequate claim scope. We propose continuing discussions on

18 this topic.

19 Section 112 issues: Sometimes it seems like
20 examiners have converted their utility rejects from "It's
21 incredible that you could do this" to "You haven't taught
22 me how to do it." If we cannot get a patent, we'll still
23 be delayed years in getting biotech patents. The
24 development of drugs today is literally an industry, with
25 regulations that stipulate when and how to do certain
26 testing. Pharmacologists are familiar with establishing
27 dosing, whether for antibiotics or other recombinant
28 proteins. Obviously, the examiners had experienced drug
1 41
1 developers, and so those topics are largely unknown to
2 them, but not to those familiar with the current state of
3 the art. Again, this is something we need to work on
4 together. Perhaps I should go back to B.I.O. and see if
5 members would have scientists to provide seminars on these
6 topics.

7 Now, for some specific steps. Step one, I
8 don't know if you realize this, but the examiners are
9 asking the inventors to send in any sequence that appears
10 in the patent application literally. If we have a new
11 hoopla of human growth hormone factor and we show a
12 comparison in the figure, they tell us to send in a
13 sequence listing, the sequence for the known human growth
14 hormone factor that already appears in Genbank and is no
15 doubt in your database already. And we see these day to
16 day. We know that your database may be very redundant. We
17 could work together on this. If we simply cite to a known
18 database location, called G.I. number for Genbank, that
19 should be sufficient.

20 Step No. 2, because of this redundancy, we
21 know that you already have a redundant sequence. So as the
22 gentleman from Maas Parr said, we need to work on that
23 redundancy. It may be double, triple, quadruple the
24 sequences it may be already. And from the pace the
25 research is going and the pace it looks like, you'll be
26 receiving a lot more sequences in the future. Streamlining
27 your database will be essential.

28 No. 3, convene a meeting on the sequence
1 42
analysis technology with industry, academic and government

2 experts. Definitely Maas Parr has some new information.
3 And hopefully working together, we can get to the goal of
4 helping you search. It would be helpful if we started an
5 information exchange, which sounds like it could be
6 beneficial, and I know you'd like to continue that on an
7 open forum, too.

8 The state of the art does appear to offer
9 software tools and help subjects to come up with all the
10 relative but not the superfluous prior art. From the PTO
11 presentation, it appears likely that inefficient searchings
12 is excessive and bogs down examiners with excessive
13 printouts and diskettes.

14 Although such a meeting should take place as
15 soon as possible, there's a big bioinformatic meeting in
16 Baltimore in early June. Maybe your schedule would allow
17 so we could help arrange or follow on or present a meeting
18 of that. All the experts are meeting in the neighborhood
19 at that time.

20 Step No. 4. Draft internal quality standards
21 for sequence searches by patent examiners just like you did
22 with the utility examiners. We should have an appropriate
23 search standard, then we'll get something we can go to the
24 bank on. Providing these examples to the public will
25 encourage biotechnology inventors to ask for rational
26 coverage and support it with the searches they routinely
27 perform.

28 And Step No. 5, after we get that expert input
1 and quality standards, let's reevaluate the cost to do
2 searches and examiners' time. And then that will be a good
3 time to have a meeting and again request the investors'
4 input to help. That will be the time to discuss additional
5 approaches, such as providing tailored searches.

6 Again, we applaud the progress that you've
7 made. We really appreciate the way you've been working
8 with us, and we look forward to cooperating on these
9 initiatives in the future.

10 MR. LEHMAN: Thank you very much.

11 Any questions?

12 I have a question relating to Incyte. I

13 appreciate what you had said about the utility guidelines,
14 and obviously as ICF being the essence of utility
15 guidelines, that you have to show that there is going to be
16 some utility, for example, in the case of biotechnology
17 inventions, that relates to the pharmaceutical, ultimately
18 what would be the disease that would be cured and so on and
19 so forth, and you have provided four mechanisms far short
20 of human clinical trials to show that utility, and so on
21 and so forth, but you've indicated Incyte is a -- I think
22 you referred to it as a genomic -- what was the word?

23 MS. LUTHER: Genomics company.

24 MR. LEHMAN: Genomics company. And the
25 applications that we're talking about are largely
26 applications that are flowing out of genomics companies
27 rather than other kinds of biotechnology companies. And so
28 first I'd like you to explain for me a little bit more what
1 the difference is between a genomics company and other
2 people in the industry. Can you do that?

3 MS. LUTHER: We have Randy Scott here who is
4 our vice president and chief technology officer who does an
5 excellent description of that.

6 MR. LEHMAN: He's on the list?

7 MS. LUTHER: Yes.

8 MR. LEHMAN: I'll ask him then, since he is
9 going to be preparing an answer for that question. And
10 maybe I should just wait until he comes to testify to
11 follow up on that line of questioning.

12 MS. LUTHER: We believe by issues of state of
13 the art bioinformatic and using the biology, we do know
14 about the sources of its sequences and the multitude of
15 comparison that we can make among all different libraries
16 that we have representing multitudes of different tissues
17 in the human body, that we can come up with a good argument
18 for utility for many of the sequences.

19 MR. LEHMAN: Thank you. Are there any other
20 questions? If not, we'll move on to Randy Scott.

21 MR. SCOTT: Good morning, my name is Randy
22 Scott. Hopefully a good part of my comments will address
23 exactly some of your questions and issues. I would really
24 like to structure this in two different parts. One, first

25 of all, is just to step back and talk a little bit about
26 what we think is the future of the vision of this whole
27 field of bioinformatics and genomics because I think if you
28 want to deal with practical problems today, it's incredibly
45
1 important to be envisioning what this world is going to
2 look like in two years so that you don't have to be solving
3 today's problems two years from now and realize that all
4 you've done is put yourself behind the eight ball in terms
5 of a whole new set of problems. So I'd really like to talk
6 a little bit about the vision that Incyte has and the way
7 that we believe the world is going to look in a few years
8 because of bioinformatics, genomics, which is now a very,
9 very important and vital sector of the biotechnology
10 marketplace.

11 To sort of give you an introduction, I'd like
12 to go back about a year ago when I was with my son, who is
13 an 11-year-old, and we went to the movie "Apollo 13," and
14 we were sitting there watching the point in "Apollo 13" in
15 which the projectory is off coming back into Earth, and so
16 they had to change that trajectory slightly. And we all
17 sort of think of NASA as this fantastic, high-tech
18 organization, and I was amazed in the movie, which was
19 quite accurate, in which the -- one of the astronauts
20 pulled out a slide rule and calculated the trajectory on a
21 slide rule.

22 Of course my 11-year-old son punched me and
23 said, "Dad, what's a slide rule?" because he's been
24 playing on computers now for most of his life and using
25 calculatōrs, and so he had no recollection of the level of
26 complexity that he has to work with in today's environment
27 versus what they had in the 1960s. And it struck me right
28 as he asked that when I was growing up in the '60s, my
46

1 parents and everybody at that time used this phrase, "Why
2 is it that we can put a man on the moon, but we can't cure
3 the common cold?"

4 And it sort of struck me right at that moment
5 that the reason is very simple. The complexity of the
6 human body and of biology and disease is in fact millions
7 of times greater than the complexity of putting a man on

8 the moon. So I think what we've looked at in medicine as a
9 very high-tech field and sector for a lot of years and
10 we've patted ourselves on the back, in fact, we at Incyte
11 believe that we're in the very, very early stages -- in
12 fact we're not high tech at all.

13 Imagine trying to play a game of cards with a
14 deck of cards in which you only have five of the cards to
15 play with. There's not many games that you can get
16 involved with. And in fact what Incyte is doing and what
17 the worldwide genome effort is doing is first and foremost
18 just trying to take apart the human body and figure out
19 what are the 100,000 genes that make us us. And in fact
20 the mechanic of your car is not going to do very well if he
21 doesn't even know all the parts that exist in your car.
22 And so until we have all of those parts and all of those
23 pieces in place, our fundamental understanding of biology
24 is always going to come far short of the absolute
25 complexity with which it exists.

26 Just to give some examples, most of the drugs
27 that are on the market today were probably developed 18 or
28 19 years ago at which time maybe only a few hundred genes
1 47
1 were even identified and characterized to any great extent.

2 As of 1990, we estimate there are probably
3 only 2,000 genes within the genome for which we had a
4 complete structure, much less much in the way of downstream
5 biological information. And yet in the last five to six
6 years, because of the advent of hybrid dna sequencing
7 technology, we've now been able to identify at Incyte
8 what's probably approaching 100,000 genes within the human
9 genome. In fact our expectations are that the level of
10 complexity we're still seeing, that there may be as many as
11 150,000 genes or more within the human genome.

12 When you think for a second that means in five
13 to six years time, we're going to go from 2,000 to 100,000.
14 That's almost two orders of magnitude increase in the
15 number of genes we now have available for researchers to
16 study. And so I think throughout the world, that's been
17 brought up as an enormously complex issue. We have to be
18 able to deal with these types of problems, not with paper
19 lists but rather with very sophisticated computer analyses

20 to be able to help us to examine that data.

21 But in fact that's only the beginning of the
22 complexity. Because the second order of complexity is not
23 just having a list of all 100,000 genes in the genome,
24 which in fact we will have and many different companies and
25 the public domain will have within the next few years, but
26 knowing which of those genes is expressed and turned on and
27 off in different phases of biology.

28 Now, if you take my prediction of 150,000
48
1 genes within the genome and you just take the position that
2 each gene is either on or off in any given cell or tissue
3 or biological environment, that already gives you any
4 number of possible expression states of the genome of 2 to
5 the 150,000th power. While that number is not infinite,
6 but it might as well be from our practical aspects of how
7 we can look at that data and yet that's precisely the goal
8 of companies like Incyte Pharmaceuticals; is to understand
9 not just the list of the 800,000 genes in the genome or
10 more but also which of those genes -- and typically it
11 maybe anywhere from 10,000 to as many as 30,000 genes that
12 are expressed in a single biological setting.

13 We don't want to know just those genes that
14 are expressed in the central nervous system. We want to
15 know the genes that are expressed at a particular time and
16 state of the central nervous system that might be
17 associated with disease. So as you begin to think about
18 the complexity that I've described here, you begin to
19 realize that computer tools and informatics are absolutely
20 the only way that we'll be able to understand this
21 complexity, so they're absolutely pivotal to how we move
22 forward as an industry and I think how the patent office is
23 going to be able to deal with the increasing complexity of
24 pharmaceutical inventions because we're going to be
25 providing you with data not from four or five genes, which
26 we've measured by a lyse analysis that predicts that one of
27 those genes is associated with, for example, Alzheimer's
28 disease or rheumatoid arthritis, we're going to be
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1 providing you with electronic, computerized information,
2 databases that suggest we've done exhaustive studies of

3 these 10,000 genes, and we can show you which of these
4 10,000 genes are up-regulated during this biological event
5 and which are down-regulated. And we can correlate that
6 with structure and with function. And we can make very
7 good predictions about which of those molecules are going
8 to be important, not just to cure the disease but to
9 understand the disease to begin with, which we think is one
10 of the primary reasons for our existence, is to be able to
11 identify markers, genes that could be used either in a
12 clinical setting, in a diagnostic setting to look at a
13 particular disease or as clues for the pharmaceutical
14 industry to be able now to exploit some cured disease.

15 Genomics, in fact, we believe -- or I
16 believe -- is simply a commercial term that is risen to
17 describe what the public sectors called the worldwide human
18 genome effort. There are two different parts to what I
19 believe are genomics. The first part is hytrobid
20 [sic] tools for studying biology thousands of genes at a
21 time. And in the early days most people recognized that as
22 hytrobid [sic] DNA sequencing. We have come up with some
23 smart ways to do the DNA sequencing, some very sufficient
24 ways to do the DNA sequencing that allow us to identify
25 expressed genes in a very, very rapid rate. But that's
26 just the beginning.

27 Once we have each gene, when we sequence it
28- the second time, we can identify the gene that we've
1 already seen, and we can be able to compare where we've
2 seen that gene before. And so we're not just doing this at
3 the genomic level. We're doing it at the level of biology.
4 We're understanding which gene is terminal and in a
5 prostate cancer sample versus a normal part of that same
6 prostate just a few millimeters away, being able to do an
7 exhaustive comparison of those two samples of which genes
8 are up-regulated and down-regulated which leads us to a
9 fundamental understanding of which genes are involved in
10 the prostate cancer process. So that's the first step
11 deciphering DNA sequencing.

12 As you may know, there are many, many
13 technologies that are being developed now which will allow
14 us to take any excessive genes that we can identify on a

15 database, put those onto literally a silicon chip or a
16 glass slide and to be able to rate thousands of clones and
17 now to be able to process multiple biological samples
18 across those thousands of clones.

19 So now after we do our initial studies, we can
20 take a thousand genes that we believe are involved in
21 prostate cancer and we can take biological specimens from a
22 variety of different individuals, and we can test that
23 hypothesis, and we can demonstrate further with clinical
24 samples which of those genes are regulated only in a
25 portion of prostate cancers and which are regulated in all
26 prostate cancers. And in fact in many diseases, we'll find
27 that there may be no single gene that correlates with that
28 disease but rather patterns of different molecules of
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1 different family's members which correlate with that
2 particular disease, and that will allow us to explore that
3 information further. In fact we believe that that's the
4 future of diagnostics, is not one molecule at a time but
5 thousands of molecules at a time.

6 How would you look at that data? How do you
7 look at data derived from searching 200 patient samples
8 across a thousand or more molecules?

9 A simple list or even a computer printout
10 profile is not enough. You have to be able to use very
11 large, very sophisticated relational databases to store and
12 allow you to search and retrieve just the bits of
13 information that you want to utilize for the particular
14 studies or for the particular analysis that you want to do,
15 which brings me to what we believe is the second part of
16 the genomics effort is not just creating a hybrid tools
17 for analyzing biology thousands of genes at a time but
18 information tools and databases, tools for mining those
19 databases that allow us to get the unique data sets that we
20 need very, very quickly.

21 This is not unique to biology. It's not
22 unique to bioinformatics. This is a wave that is taking
23 over the entire economic sphere of our country -- database
24 mining. As we're able to store larger and larger amounts
25 of information, the tools now for mining those data sets

26 and being able to create usable information are enormously
27 valuable. And I would submit that one of the things that
28 the patent office needs to be thinking very seriously about
1 is moving towards electronic filing.

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2 As we file large number numbers of patents
3 with large numbers of CDC sequences in those patents, that
4 paper stack cannot even begin to explain the complexity of
5 the database from which it was derived and our ability to
6 search that database to compare the sequences against each
7 other and get results within seconds, not hours or days.
8 And our ability to compare where each gene and each
9 individual biological setting is as expressed, that
10 information is only going to explode over time.

11 Our database currently houses several
12 megabites of information, but we see that whole field
13 expanding by orders of magnitude in complexity over the
14 coming years. You never use all of the data all the time.
15 No biologist is trained to be able to sit down and use all
16 of that information. You're only able to mine that
17 information for the observations that you want to follow up
18 on.

19 So the implication for biologists, and I think
20 for many scientists, is that our whole world is going to be
21 changing over the next several years. We don't think
22 bioinformatics is simply a tool that a few specialists will
23 be using. We believe it will be the primary basis in which
24 biologists will be able to retrieve, do searches, analyze
25 and set up their individual experiments.

26 At Incyte, we draw a lot of analogies for our
27 business to the computer industry with its emphasis in both
28 hardware and software. For us, hardware means that first
1 part of genomics, hytrobid tools for analysis. Our
2 hardware is DNA sequencing and tools for analyzing DNA
3 samples or sequences at a very, very rapid rate.

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4 Today at Incyte, we're sequencing between
5 6,000 to 7,000 cDNA clones per day. That's an enormous
6 array of sequencing. In fact, we believe that there's
7 probably a corollary between Moore's law and the
8 semiconductor industry and what we're doing today in DNA
9 sequencing. That is, we double the rate of sequencing at

10 Incyte and have doubled it almost every six months since we
11 started the company down this path in 1991.

12 If I'm correct with that, that means from 6-
13 to 7,000 sequences that are being analyzed a day, we'll
14 have to process 12,000 or more in six months, 24,000 per
15 day six months after that. And algorithmic expansion, of
16 course, means we have to build all the tools to do that.
17 In fact I would argue that we've done that in a very, very
18 satisfactory fashion. So let me just give a brief
19 explanation of the bioinformatics tools that we use in
20 house.

21 And I think the philosophy or the theory comes
22 back to database mining: Don't try to create a large set
23 of data about every single molecule that you're going to
24 look at. Select your questions very carefully. We tell
25 our scientists all the time, "Be careful what you ask for
26 because you may get it." So if you ask for an
27 all-encompassing report of every sequence, you will get
28 that, and you will be so overloaded with information, you
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1 could never analyze it, and the whole system will grind to
2 a halt.

3 So in our system we take some very
4 straightforward approaches. First, do the easy searches
5 first with the fastest tools and the easiest tools, ones
6 that don't take the computer intensity of time. So within
7 our process we can search and analyze about 6,000 sequences
8 a day in a pretty straightforward process in which, first,
9 we take every one of those sequences, and we go through a
10 series of masking programs, and we eliminate all the things
11 that we know we're not interested in like repetitive DNA
12 elements, alpha sequences, things that are not useful
13 information because they've been sequenced many, many times
14 over -- there's nothing inventive about that process. But
15 there's a key reason to do that is because when we now turn
16 around and search our sequences against the public domain,
17 if we don't remove the so-called junk sequences out of our
18 information, what we'll find is that our junk will match up
19 with public domain junk and you end up with junk squared.
20 And that's not good. So you want to get rid of at least --

21 have at least one data step in your comparison set in which
22 you've removed all that and we go so far as to mask things
23 like dinucleotide or trinucleotide repeats, so we get down
24 to the sequences, just the things that we're really
25 interested in.

26 Then we go --

27 MR. LEHMAN: How do you distinguish between
28 the public domain and what is yours?

1 MR. SCOTT: Well, that actually comes in a 55
2 second phase of the analysis. In the first phase of the
3 analysis, we've worked with numerous academic
4 collaborators, probably many of the same people that you
5 would find available for consulting roles to set up
6 databases of all of the mitochondrial genome, the
7 ribosomal genome, almas, repetitive almas. We've
8 established what those outside collaborators -- Temple,
9 Smith and Boston University was one of the founders of
10 Genbank, Jean Claude Rabore [sic] of the CNRS and many,
11 many other scientists' parameters that are fairly widely
12 agreed upon in the bioinformatics community to be able to
13 eliminate those elements first.

14 MR. LEHMAN: Well, is your distinguished -- is
15 what you distinguished between being the public domain and
16 what is yours then simply what has previously existed --

17 MR. SCOTT: That's --

18 MR. LEHMAN: -- prior to your --

19 MR. SCOTT: That's correct. That comes in the
20 second stage -- phase of the analysis. Once we've
21 eliminated those, probably for our purposes, more
22 uninteresting molecules, we do a very fast search, which is
23 called a blast search. That's -- we can set up multiple
24 sequences processed in batch mode. It's not the best
25 searching algorithm, but it is the fastest. And you can
26 search huge volumes of sequence information very, very
27 quickly. And the only question we're asking is: "Do we
28 have an exact match to Genbank primate?"

1 We don't need to look at C elegans. We don't 56
2 need to look at yeast. We don't need to look at bacteria
3 because we know that our feed sequence comes from humans,
4 and so we simply look first for an exact match in a very

5 small portion from Genbank. And over half of our sequences
6 are immediately caught through that process as exact
7 matches. And so we can eliminate those right off the bat.

8 And then we can take the remaining sequences
9 and just start to do more in-depth searches. We can say,
10 "Okay. Now let's look for homology in the human primate
11 database or" -- first what we do is we go to rodent
12 database and we say, "We have something that is very
13 closely aligned to a mouse or rat sequence" because, again,
14 that allows us to identify "This looks like the human
15 correlate to a known mouse or rat gene."

16 Then we can go back and use more sophisticated
17 tools to look for homologies. And I would suggest that
18 that in fact is one of the approaches that the patent
19 office would want to take, is to do the easy things first.
20 Come up with ways that will allow you to screen and sort of
21 immediately eliminate half of your work load or more. Then
22 only come back to the narrow subset of things for which you
23 want to go in much greater depth and use the more
24 sophisticated algorithms such as the Smith-Waterman
25 algorithm I believe is running under Maas Parr instruments
26 to do that second process.

27 So by going through these stages, Incyte
28 actually does, I think, a very high-quality job at cleaning
1 up, comparing things to the public domain -- first simply
2 identifying what's an exact match and what is not and then
3 going through a process of trying to annotate those
4 molecules that are not exact matches to show what are they
5 most structurally related to and then from then on we can
6 select from molecules that we think are highly related or
7 are highly up-regulated in certain biological cases to
8 really hone in on the individual value of those molecules.

9 That system is now in place and has been
10 running since September of 1995. So well over six months
11 it's actually been put in place in collaboration with the
12 collaborators, as I mentioned, many of them who are free to
13 consult and work with other groups and in fact we would
14 quite encourage you to have some of those groups in because
15 our daily life is surrounded by, you know, the process of

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16 information. We don't do it -- if we don't do it in a
17 rapid time frame, we won't exist because we can't present
18 this information in our database for pharmaceutical
19 partners. So I think I can probably go on for some --
20 MR. LEHMAN: I'd like to ask. What is -- how
21 long has Incyte been in existence?

22 MR. SCOTT: Since April 1991. How far along
23 was our corporation.

24 MR. LEHMAN: And do you have sales right now?

25 MR. SCOTT: We do have sales. We have six
26 database subscribers, which are some of the six -- some of
27 the best pharmaceutical companies in the world -- Pfizer,
28 the pharmacy at Upjohn, Nomen Ordiz, Johnson & Johnson and
1 Abbott Pharmaceuticals. Our current annual revenue rate
2 from sales of the database is in the range of \$25 million
3 per year. So in fact as I look more and more at the
4 software and informatics sector, there's an awful lot of
5 software and database companies out there from other fields
6 that don't yet add up to 20- to \$30 million in revenue.

7 Our marketplace, we believe, is the top 50
8 pharmaceutical companies in the world, to get this
9 information into their hands as rapidly as possible. They
10 have accessed our intellectual property portfolio. All of
11 those companies have nonexclusive access to the use of our
12 sequences for research purposes and then exclusive access
13 on a first-come, first-serve basis to individual gene
14 product patents that might derive from our work. So in
15 fact we are creating sort of a unique resource for the
16 pharmaceutical world. And in many ways, patents are almost
17 more important to us because what we're selling is ideas.

18 MR. LEHMAN: When you talked about how you do
19 your work, you said that you start out comparing your
20 genomic mapping to what's in the public domain already, and
21 you identified that as basically work that's already been
22 done by other people, largely academic scientists.

23 What kind of reciprocal relationship is there
24 between you and them? Let's say, you know, the scientist
25 at Harvard wants to follow up on research that he has done.
26 Do you have relationships with them? Do you share
27 information with them? And if you do, what kind of terms

28 and conditions do you apply to them?

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1 MR. SCOTT: We actually do so, but we do so
2 indirectly because we don't really regard this database as
3 ours. We regard it as our pharmaceutical partners. So
4 almost all of our pharmaceutical partners in fact have
5 programs by which they interact with the academic
6 community. We quite encourage that. So while we do have
7 some individual academic collaborations -- one, for
8 example, is an institution by the name of Mayo Clinic by
9 which their researchers at the Mayo Clinic can get access
10 to full-length clones that derive from Incyte database
11 through collaboration there. Most of our academic
12 collaborators go to the pharmaceutical companies themselves
13 because it often turns out that they, like we, are looking
14 for capital to fund their research. And capital, you'll
15 find, is not within the biotechnology companies but within
16 the large pharmaceutical companies that are really
17 developing and dropping off of this business.

18 So we think in fact there is a tremendous
19 synergy here. In essence, the pharmaceutical industry is
20 paying Incyte to very rapidly try to create some of this
21 information ahead of time to come into the public domain.
22 And so by funding that program, they're both accelerating
23 the pace of research, and they, as they look through the
24 database and work with their own academic collaborators,
25 can identify individual molecules that they now want to
26 pursue more aggressively and encourage --

27 MR. LEHMAN: Would you say that what --

28 primarily what you're doing is creating a database on a
1 human genome?

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2 MR. SCOTT: Absolutely. I think Incyte is an
3 informational technology company.

4 MR. LEHMAN: And that database is used as a
5 tool, or when you speak of "tools," are you speaking of
6 something different from the use of the database?

7 MR. SCOTT: No -- well, I think the tools are
8 many fold. They're not just the database. They're --
9 they're the database, the proprietary software we've
10 created around the database to be able to help them mine

11 hat database and the actual molecules themselves. Because
12 what's unique about Incyte is that not only can you search
13 through the database to find a molecule, it's not coming
14 out of an archive like Genbank, where now you have to go
15 track the original reference source to find out if they're
16 even willing to give you material. Our pharmaceutical
17 partners immediately have access to every gene for which we
18 have a cDNA stored away that we provide within days after
19 that. So they're also requiring access to new receptors,
20 new targets, and they have access also to the intellectual
21 property portfolio and the molecules for which we're filing
22 patents on.

23 MR. LEHMAN: Are you filing patents in other
24 countries besides the United States?

25 MR. SCOTT: In other countries, we're filing
26 patents on full-length clones only and being very selective
27 about how we filed on EST sequences, primarily because of
28 the publication rules because we believe that our economic
1 value and what we're being paid for primarily by the
2 pharmaceutical industries is for lead time. And that's
3 true of almost all pharmaceutical research. They know
4 that ultimately every pharmaceutical company will have the
5 same genes and the same products, but if they could get a
6 lead time past their competitors, then they can move very,
7 very quickly. So anything that of course puts all of our
8 information into the public domain simply means that the
9 capital resources for doing this will dry up because --

10 MR. LEHMAN: One of the -- you -- sounds to me
11 like fairly accurately compared what you're doing to the
12 more classical software industry and that in fact there is
13 sort of a merger going on here between software and biotech
14 industries and what you're doing, and of course the
15 software industry has for a long time kept the light on
16 multiple forms of intellectual property protection and not
17 simply patent protection, to rely on copyright protection
18 as well.

19 Copyright does not protect what is just pure
20 information, however, and thus the Supreme Court has
21 decided that pure information in the form of database -- a
22 database -- even with that database is very difficult to

23 create and requires a lot of investment that has no
24 protection.

25 This is a global problem, not just a U.S.
26 problem. And in fact the European commission is in the
27 process of promulgating directive to all the members states
28 to the European union to enact laws which would provide a
1 new kind of intellectual property protection for --
2 specifically for databases, even though they don't meet the
3 test of what we call originality in our copyright sense.

4 MR. SCOTT: Right.

5 MR. LEHMAN: But it would be more of a
6 copyright-like type of protection as opposed to a patent
7 type of protection. Really protects the information in the
8 database and from unfair extraction or unfair exploitation
9 of that information.

10 Would that be something that would make your
11 life -- and it's easier -- it would be easier to get, by
12 the way, because then you wouldn't have to apply for
13 patents and, you know, spend all the money and spend a
14 couple years trying to deal with the issues that we're
15 talking about here today. Would that sort of protection be
16 something that would be welcomed for you?

17 MR. SCOTT: I think on the databases as a
18 whole, certainly would allow me to sleep easier at night to
19 know that we have some level of protection should that
20 database ever be stolen or, you know, other sorts.

21 MR. LEHMAN: Particularly important in a
22 computerized environment because in the old days when you
23 had databases that were contained on paper basically, you
24 know, just physically there was a certain protection. You
25 know, you couldn't --

26 MR. SCOTT: Right.

27 MR. LEHMAN: -- you couldn't go in and copy
28 stuff out of it but obviously now where databases are
1 available electronically, you can -- if you can enter into
2 the database and enter into the security that may have been
3 provided by incryption, you can, you know, extract
4 information from it, and of course nobody knows where you
5 got the information.

6 MR. SCOTT: I think absolutely that would be
7 welcomed. It probably wouldn't change the patent stance
8 because, I mean, we really are a merger between computer
9 science and microbiology, and the value, the information
10 now leads you to which molecules you want to take forward
11 into product relationships, whether it be diagnostics or
12 therapeutics. So I don't think it would be looked at as a
13 solution to the patent dilemma of the patenting of
14 thousands of molecules at a time. And the other thing,
15 this dilemma that we're now seeing in the patent office
16 with the number of molecules that are being discovered is
17 really -- it's the embarrassment of riches or the fact that
18 such a wealth of information can be created, everyone knows
19 it's so enormously valuable in such a short time, I think,
20 is much of the -- much of the shock.

21 So still individual molecules are something
22 that we would continue to pursue. We have a whole group of
23 biologists that we call the Group in Silico, biologists --
24 for years people have done in vitro and in vivo biology, we
25 think the state of the art now is so good with
26 bioinformatics that -- certainly not for all, not even for
27 most, but for a large number of molecules there is a clear
28 structure-function relationship that's been hammered out in
1 the laboratory. And now we can identify members of this
2 family. And even more importantly than that, it's highly
3 up-regulated in the joints of arthritis patients. So we
4 believe this is a clear-cut observation and be able to
5 provide this molecule in a way in which the pharmaceutical
6 sector can both have intellectual property protection on
7 the molecule and be able to pursue those aggressively, I
8 think, is going to be tremendous value to society.
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9 I think people will be shocked at the amount
10 of knowledge of disease processes, of the most complex
11 disease processes we haven't been able to get at by doing
12 biology one at a time like cancer, AIDS, writing different
13 viral settings as well as arthritis. These are complex
14 diseases probably with multiple etiologies, multiple
15 genetic makeup and background and will not fall into one
16 disease category. And it won't be until you break those
17 apart into 10, 15 separate disease categories and different

18 treatments and regiments that we're really going to be
19 successful in curing them.

20 So I see tremendous value added over the
21 coming years, not just by Incyte or our colleagues and
22 competitors in the genomic sector but now as pharmaceutical
23 companies really come into this field in a big way to be
24 able to exploit the information and develop drugs.

25 MR. LEHMAN: Are there any other questions?

26 Thank you very much.

27 Next Michelle Duran.

28 MS. DURAN: I signed by mistake.

1 MR. LEHMAN: Oh, so you're not planning to
2 appear.

3 Ned Israelsen.

4 MR. ISRAELSEN: Good morning. Thanks for the
5 opportunity to testify at these hearings. My name is
6 Ned Israelsen. I'm a partner with the law firm of Knobbe,
7 Martens, Olson & Bear. I head up our biotechnology group.
8 The address of our local office here in San Diego where I
9 work is 501 West Broadway.

10 And I'd like to focus my remarks specifically
11 on the questions that were proposed in the Federal Register
12 in August and try to provide the views of my law firm, and
13 I'll emphasize that these are not necessarily the views of
14 our clients on the problem facing the patent office right
15 now.

16 Seems to me that it would be unfair to make
17 all biotechnology applicants pay for a problem that's the
18 result of a handful of patent applications. And so at the
19 risk of offending those companies that are filing the
20 patent applications, I think that the cost should be
21 allocated based on the patent office resources that are
22 consumed by these patent applications with large numbers of
23 sequence.

24 I have some personal experience in looking at
25 this issue. I was involved in filing some patent
26 applications for the National Institutes of Health and
27 became rather notorious with thousands of EST sequences,
28 and I'm not saying that I was -- I was very surprised that

1 we did not get a thousand way restriction requirement back
2 from the patent office.

3 It seems that the patent office when faced
4 with a large number of sequences that are related only in a
5 general way, already has a tool for -- for dealing with
6 collecting fees commensurate with the amount of work
7 required for examination.

8 Another alternative that I could suggest,
9 aside from restriction requirements, would be a surcharge
10 if considerable resources are going to be consumed by a --
11 for examination of a particular patent application. A
12 surcharge could be imposed, but I think only after giving
13 the applicant an opportunity to amend the claims.

14 So what I would envision is that the examiner
15 takes a first cut at looking at the claims, looking at that
16 amount of searching that will be required, coming up with a
17 total amount and an explanation of why considerable
18 searching would be required and then giving the applicant
19 an opportunity either to amend the claims or to pay the
20 additional search fee.

21 I have been surprised, again, with some patent
22 applications I filed where a claim that we really don't
23 expect to get is thrown in for sake of completeness that
24 says, for example, an 8 MER or an 18 MER or 15 MER of the
25 full length sequence that we really want to patent. My
26 understanding is that considerable amount of search
27 resources can be used looking for those short sequences
28 when ultimately those have only an ancillary importance to
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1 the applicant and if given the choice between paying a fee
2 to have a massive search conducted or forgoing the claims
3 for the short sequences, I think a lot of applicants would
4 forgo that broader search. So the search could be
5 attenuated even before it started by giving the applicant
6 the opportunity to amend.

7 Echoing another approach the patent office
8 could take -- and it's already been suggested -- is to keep
9 the database size down by eliminating the need to submit
10 known sequences and unclaimed sequences, in other words, to
11 allow reference, for example, to a Genbank sequence instead
12 of submitting that sequencing electronically once again and

13 providing multiple copies in the patent office database.
14 And again the requirement that sequences of 10
15 bases or four amino acids be submitted is a burden to
16 applicants and I think, again, clutters up the database.

17 As to a long-term solution, I've given a lot
18 of thought to patenting of naturally occurring sequences,
19 and I concluded that the current patent system is not well
20 suited for handling naturally occurring sequences that are
21 cranked out in the thousands or tens of thousands at a
22 time. I know there has been concern expressed by
23 scientists working in a field that the rewards of a patent
24 for -- are not necessarily commensurate with the value
25 provided when a genomics company is allowed to get a patent
26 on a sequence based on a very minimal utility.

27 So one suggestion that I have espoused in
28 recent years is a registration system similar to copyright
1 68
2 for providing some sort of protection for sequences that
3 come out of massive sequencing efforts, naturally occurring
4 sequences. Perhaps that registration system could provide
5 only a defensive right, again, subsequent patents and could
6 also provide perhaps a transferable exclusion of that
7 sequence from the prior art. So that when a utility is
8 determined -- that fits into the more traditional
9 categories that one would anticipate for a patent such as
10 the use of a particular molecule for treating a particular
11 disease or a particular diagnostic application, the
12 prior -- the exclusion from prior art would provide the
13 ability to subsequently patent that sequence for its
14 biological use or for a use related to the protein encoded
15 thereby and the prior publication, the publication of that
16 sequence subsequent to its discovery and registration but
17 prior to the patent focusing on the biological utility
18 would not provide a barrier to getting more traditional
19 patent protection. So those are my thoughts. If there any
20 questions, I'd be happy to entertain them.

21 MR. LEHMAN: Thank you. You heard me talking
22 about the European database with the previous witness, and
23 that sounds like that's sort of the direction of what you
24 were talking about there.

24 MR. ISRAELSEN: It's a similar idea, yes.
25 MR. LEHMAN: Of course, one of the -- that is
26 more of a copyright-based approach, and that doesn't give
27 you any exclusivity vis-a-vis independent creation of the
28 same database.

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1 MR. ISRAELSEN: That's correct.
2 MR. LEHMAN: Should it?
3 MR. ISRAELSEN: That's a -- that's a loaded
4 question, and I'm probably not the best person to answer
5 that. With my proposal for a registration system for DNA
6 sequences that are naturally occurring, it would not give
7 exclusive rights. It would not give the right to exclude
8 others but would help preserve the option of obtaining a
9 patent at a subsequent time.

10 MR. LEHMAN: Okay. Are there any other
11 questions?

12 MR. GOFNEY: Yeah, I wanted to ask him
13 whether he had any criteria when a search -- a surcharge
14 might be required.

15 MR. ISRAELSEN: I don't know the economics,
16 but I would expect that it would be imposed only on a very
17 small percentage of applications so that an application
18 containing -- just to pick a number -- 50 sequences would
19 not incur the surcharge.

20 MR. LEHMAN: Are there any other questions?
21 Thank you very much.

22 MR. ISRAELSEN: Thank you.

23 MR. LEHMAN: We appreciate it. I want to
24 thank the -- particularly the practitioners who came and --
25 oh, we have one more.

26 Amy Hamilton.

27 MS. HAMILTON: Good morning. My name is
28 Amy Hamilton. I'm from Eli Lilly & Company. My views do
1 70
1 represent those of the company. Our address is Lilly
2 Corporate Center, Indianapolis, Indiana 46285.

3 I hadn't planned on speaking today until I sat
4 there and heard nothing but restriction requirements, and
5 then I was thankful to hear Mr. Israelsen mention that
6 because I really think that's incumbent upon the PTO to
7 take applications where there's no overriding, nontrivial

8 utility to unify the sequences that clearly the law
9 requires that they be treated as separate inventions. And
10 then when that is done, GACT, and its ramifications will, I
11 think, cause these companies to properly file these as
12 separate applications.

13 I would also recommend some kind of a
14 surcharge for a huge number of sequences. We have thought
15 about, again, some charge appropriately determined by the
16 PTO, something similar to what is done with claims above
17 some reasonable number of sequences. I think 10 is a
18 reasonable number because for a single invention, it's hard
19 to imagine why you would have more than 10 sequences in
20 that application. I'd also like to challenge what was
21 stated in the OT about requiring completeness of
22 examination. 37 CFR Section 105 allows for incomplete
23 examination when there is misjoinder invention or
24 fundamental defects in the application. And I would
25 suggest that cases could be reviewed for a threshold
26 utility before ever making a search, which I think of all
27 things should drastically decrease the amount of computer
28 searching. Then this could be challenged in the courts,
1 and we could get the utility question resolved in the
2 courts, as we are going to eventually need anyway.
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3 One last thing, 1800 examiners continue to
4 make rejections based on potential methods of making genes
5 and proteins. This form of rejection has been explicitly
6 stated as improper by the CAFC in a series of cases ending
7 in *in re: Bell* and *in re: Dual*. This is prolonging
8 examination and taking up valuable examiner time when there
9 is no prior art chemical structure to be used in the
10 rejection, and I would suggest that valuable examiner time
11 could be saved by eliminating this type of rejection.

12 That's all I have. Thank you.

13 MR. LEHMAN: Thank you very much. Did you
14 give us your address where you were located?

15 MS. HAMILTON: I did. I will again. Eli
16 Lilly & Company, Lilly Corporate Center, Indianapolis,
17 Indiana.

18 MR. LEHMAN: You came all the way out.

19 MS. HAMILTON: I wanted to come to the first
20 one.

21 MR. LEHMAN: Thank you very much. We really
22 appreciate it.

23 I believe that completes -- unless someone
24 else signs up, that completes the list of persons who've
25 asked to testify. Does anybody else like to --

26 MR. O'HARA: I have maybe one comment. I
27 didn't sign up. My name is Patrick O'Hara. I'm from a
28 company called Zymo Genetics, and that's Z-y-m-o Genetics
1 in Seattle, Washington, and we're a customer of Incyte's.
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2 And I just wanted to make a reality check on
3 the amount of time that you're thinking of that it's going
4 to take to do the searches because we do quite a of
5 searches ourselves, and I think that you're talking about
6 having 200,000 sequences that you have to search and it's
7 going to cost about \$24 million and take two years and nine
8 staff years to deal with it, and I think that Randy said
9 they can do 6,000 a day using blast as an algorithm, and
10 the question, I guess, is blast sufficient for the kind of
11 things that you have to do?

12 The person from Peterson & Associates said
13 that very sensitive kinds of searches may not really be
14 necessary for the kinds of obviousness criteria that you
15 have to look at. So it seems like what might be possible
16 to do would be that the PTO simply develop a very specific
17 criteria of what it is that is invent- -- invent- -- sorry,
18 invented with regard to the ESTs, and we at Zymo Genetics,
19 do about -- we don't -- we don't do 6,000 a day but we do
20 about 1500 a day. And so if you are able to eliminate 90
21 percent of your problem, instead of being 24 million would
22 be 2.4 million, instead of two years, would be 4.8 months
23 and at about 1500 a day, that would kind of do it, and I
24 think that with blast and related algorithms, plus some
25 post processing of the results, you'd be able to come up
73
1 with a very nice output that would pretty much
2 automatically determine what it is that you're looking at
3 in most of these EST applications. And I think it would
4 decrease the number of staff years that you're talking
5 about as well. So while with regard to the kinds of

3 algorithms that you would have to use, ESTs are parts of
4 genes, and there are specific issues with ESTs that mean
5 that certain kind of algorithms have certain kinds of
6 problems. So, for instance, there's partial overlaps that
7 will give you very different scores than complete overlaps.
8 There are certain issues with regard to accuracy in the
9 database and with regard to the ESTs, and those can cause
10 drastic differences in scores, but, however, those things
11 can all be handled pretty much automatically at a rate of
12 at least 1500 a day.

13 So it seems to me those problems should be
14 manageable by developing criteria very specifically, and
15 then perhaps contract out the searching so that the PTO
16 with the many kinds of searches or your type with 10
17 sequences or so, but when you're talking about those mass
18 ESTs, contract it out, develop the criteria and contract it
19 out.

20 MR. LEHMAN: Thank you very much. I
21 appreciate that.

22 Are there any other people who wish to be
23 heard? If not, again, I want to thank the people who took
24 the time to come here, particularly individual
25 practitioners who obviously could be doing other things,
26 and note that we're having one further hearing on this. We
27 came here to San Diego because this is a center of the
28 biotech industry. We wanted to make it easier for people
1 to come here as opposed to come all the way to Washington,
2 but we will be having a hearing on April 23rd in Arlington
3 for anybody who has some comments between now and then
4 wants to get on the plane and come to Washington, but of
5 course we're also happy to receive any further written
6 comments, and we would appreciate it if those would be
7 submitted by April 23rd.

8 A transcript of this hearing will be made
9 available as soon as it's ready as well as all of the
10 comments received. And we think that's going to be on or
11 about May 13th, 1996. And it will be available for
12 inspection in Room 520 of Crystal Park One, 2011 Crystal
13 Drive in Arlington, Virginia. And it will also be

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14 available on the Internet through a nonfile transfer
15 protocol. The address is ftp.uspto.gov.
16 All written comments and oral comments made
17 here today will be taken into consideration before
18 implementing policies relating to this issue. And any
19 written comments that are received after the 23rd can't be
20 assured of consideration. I have to say that we really try
21 hard to give people a chance to have input, and then after
22 we're six months into a new policy and somebody says,
23 "Well, you didn't consider this or that," we have not yet
24 had a patent application that gets us access to
25 impressions, so we really need to hear from people if we're
26 going to take their views into consideration.

27 So I'd like to remind everybody that another
28 hearing will be heard on April 23rd starting at 9:00 a.m.,
1 and that will be in the commissioners conference room,
2 Suite 520, Crystal Park One, 2011 Crystal Drive, Arlington,
3 Virginia. And that concludes the hearing. And I thank
4 everybody that participated and shared their views with us.

COPY

UNITED STATES DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

PUBLIC HEARING ON PATENTING OF
NUCLEIC ACID SEQUENCES

Crystal Park Two
2121 Crystal Drive
Commissioner's Conference Room
Suite 912
Arlington, Virginia

Tuesday, April 23, 1996

The hearing in the above-entitled matter,
commenced, pursuant to notice, at 9:00 a.m.

B E F O R E:

BRUCE A. LEHMAN
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

LAWRENCE J. GOFFNEY
Acting Deputy Assistant Secretary of
Commerce and Acting Deputy Commissioner
of Patents and Trademarks

EDWARD R. KAZENSKE
Deputy Assistant Commissioner for Patents

STEPHEN G. KUNIN
Deputy Assistant Commissioner for Patent
Policy and Projects

NANCY J. LINCK
Solicitor

ORAL TESTIMONY BY: _____ **PAGE** _____

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Staff Scientist/Patent Liaison
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Research Triangle Park, North Carolina 27709. . 37

Michael Fannon
Human Genome Sciences, Inc.
Director of IS Department
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 Herb Jervis
 Smith-Kline Beecham. 57
 Albert Shpunoff. 70

P R O C E E D I N G S

MR. LEHMAN: Good morning.

My name is Bruce A. Lehman. I am the Assistant Secretary of Commerce and the Commissioner of Patents and Trademarks.

Joining me at this Hearing today are Lawrence J. Goffney, to my immediate left, Acting Deputy Assistant Secretary of Commerce and Acting Deputy Commissioner of Patents and Trademarks; Edward R. Kazenske, Deputy Assistant Commissioner for Patents, on my immediate right; Stephen Kunin, Deputy Assistant Commissioner for Patent Policy and Projects, on my far left; and Nancy Linck, the Solicitor of the Patent and Trademark Office.

This is a hearing to receive public comment on a serious problem that is currently facing the Patent and Trademark Office related to patent protection for nucleic acid sequences. The public was invited to comment on this issue in a notice that we published in the Congressional Record on March 12, 1996.

For over a decade, the PTO has been examining and granting patents to claims reciting nucleic acid sequences. Scientific and technological advances have permitted rapid identification of large numbers of genes or gene fragments. The ease of utilizing automated techniques for sequencing nucleic acid fragments has resulted in the filing of a growing, although still relatively small number, of patent applications, each of which claim thousands of nucleic acid sequences. Statistics reveal that the number of these applications is growing and based on the number of organisms and genes still to be discovered, such growth will continue for the near

future.

In Fiscal Year 1991, the Scientific and Technical Information Center of the PTO searched about 4,000 sequences. In Fiscal Year 95, they searched about 22,000 sequences. Currently, we have over 200,000 sequences claimed in at least 70 patent applications awaiting search and examination.

Our estimates show that the search of 100 sequences requires about 15 hours of computing time but the evaluation of the search results for those 100 sequences requires about 65 hours of examiner time. The PTO currently has two massively parallel processor computers and could run the searches in about two years, with the computers running twenty-four hours a day, seven days a week. To examine this relatively small number of patent applications only with respect to the prior art, however, would require over 90 senior-level staff years. Thus, in order to process these applications, the entire staff of the Biotechnology Patent Examining Group 1800 would have to work for more than nine months exclusively on these applications.

These applications present a challenge to the PTO and we need help and suggestions on how we can address this problem. The United States is a leader in the rapidly growing field of biotechnology, which is a growth industry important to the economic health of this country.

The PTO has taken a very active role in working with its customers to simplify policies and procedures in ways that encourage and promote the growth of this industry. We are committed to improving the responsiveness of the PTO to its customers and to more effectively address the needs of the industry.

We must find ways to search and examine the pending applications and provide these applicants with the appropriate patent protection

for their inventions without creating an imbalance in the appropriation of the resources within and among the technologies and Patent Examining Groups. The policies established must permit the timely and thorough examination of all applications which require the same resources for completion.

We are currently working in partnership with the applicants of these applications in order to explore innovative mechanisms and to accomplish the required work in processing the applications. We appreciate the time each person who is here today has taken to attend the hearing and to provide us with your input into the solutions to these problems.

A transcript of the hearing will be prepared and will be made available for purchase by the public approximately 10 days after this hearing. Copies will also be available directly for purchase from the stenographer.

The name of the stenographer service today is Miller Reporting Company. Their telephone number is (202) 546-6666. That is Miller Reporting, (202) 546-6666. I assume you can probably talk to the stenographer here too about that.

We have received eleven written comments and seven requests to appear orally this morning. However, any persons who wish to speak and who have not previously informed us of their desire to testify are encouraged to add their names to the list located at the credenza at the rear of the room.

In order to permit all persons requesting to appear orally, including those people that may be signing up today to present testimony, we would request that each speaker limit their comments to 15 minutes. You don't have to take your full 15 minutes keep in mind.

Those persons who wish to provide

additional comments must submit their comments to us in writing no later than April-- well, that is today, April 23rd-- no later than today. The speakers have been listed in the order in which the requests were received by us.

You may also pick up at the table at the rear of the room copies of the "Official Gazette", publication of the Notice of the Hearings, and the Request for Comments on the issues relating to patent protection for nucleic acid sequences.

When you present your comments, we would request that you please give your name and address and tell us whether these comments are your own, or whether they are those of your law firm or company, or whether you represent an organization and are presenting comments on their behalf.

We would appreciate it also if the comments could be limited to the questions that were presented in the Federal Register publication of March 12, 1996.

The first speaker that we have listed is Michael Langan, but I was informed that he doesn't appear to be here yet.

Is Michael Langan here?

(No response.)

MR. LEHMAN: If not, is Margaret Smith here?

MS. SMITH: Yes.

MR. LEHMAN: Why don't you come forward, Ms. Smith?

MS. SMITH: My name is Margaret Smith and I represent Genetics Computer Group, GCG. I am the chief operating officer and one of the owners and founders of GCG.

The mission of GCG is to serve biologists by discovering, implementing, publishing and supporting algorithms in the area of sequence analysis. This is the only thing that we do. This is our main focus.

We also think that standards are very

important, and that is one of the arguments that I would like to use as a basis for my comments. And that is that what standards, such as GCG, which is widely used for analysis and searching, also as a central management tool for public databases, that are installed locally, built on standards using Fortran, C motif, runs on standard platform, such as Sun, SGI and Digital, and also incorporates standards such as Fas Day, Smith Waterman, Blast, SRS, the public databases like GenBank, PIR, Swiss Prot, EMBL, other important files like Rebase and Procite, as well as standard comparison tables.

The software from our company is also a standard on which other people build tools. Within institutions there are modifications so that longer sequences can be used or that searches can be run in a different manner or a set of searches can be run in a certain way.

The GCG software has also been a platform upon which other tools have been built.

For example, in Europe there is something called extended GCG, which is another package built on top where there are modifications and extra programs.

Compugen has built a strategy. Compugen, which is another company, has taken the basics and looked at the problems of high throughput and how to speed up searches and therefore taken the problems that are probably very similar to the Patent Office that are faced by the pharmaceutical companies and other high throughput laboratories where many sequences must be analyzed.

Also, based upon our standards, our standard package, people are building interfaces so that users, scientists, can access just the programs of interest.

The European patent office, for instance, uses our software and has a set menu that their examiners use and therefore they are limiting and

just using the part of the package that is most appropriate for them.

So, the basis of the argument is that there is a set of standards and we have incorporated many of the standards and become a standard.

I would like to specifically address the issues of the search strategy. As I mentioned before, the pharmaceutical companies face this issue, and there is a proposal of a filtering system. If you have a lot of sequences to go through, that you can first, I will give the analogy, it's like a coarse grain filter that is very quick. Things move through it very quickly, but you will catch the most obvious.

An example might be blast, the blast algorithm.

Then moving on to things that are more particular, the next part of the filter, would be something along the lines of Smith Waterman or Fass Day perhaps. And the next level of filter could be something like frame search, which is a program that allows you to take a protein sequence and search against a nucleic acid database or vice versa.

I think an important part of this filter system is to have machine readable output. There are standards. The tools to make up the filter are there, but I think the part where it's new research is needed -- not necessarily research, but new work is needed, is to look at it in terms of machine readable output and also normalization, so that there can be an acceptable level of identity before moving on to the next step in the filter. An acceptable level of identity is recognized.

I know that some of the issues seem to deal with ambiguity within sequences and there are also some other programs that can deal with ambiguity within sequences, such as Profile Search, which allows you to indicate regions of high

ambiguity or regions of high stringency before the search is done. There are also pattern matching searches that can be done.

There is really probably a circumscribed set of tools that can be placed in different slots of the filter, depending upon what the problem is. But I think the common theme is machine readable output, as well as normalization of scores.

There is work being done on this already, but I think that this high volume of data that is coming, even though we projected that it would come, everybody, not just GCG, projected that it would come, we are still caught off-base by how quickly it has come.

So, work is being done by us and by others on machine readable output, as well as normalization scores, and I think a lot of that work has been done already.

I would also like to suggest that based on the last ten years of experience that the Patent Office has had with sequence patents, perhaps guidelines can be provided for customers to provide a better set of prior art searches results that the applicants have done and can be submitted with the application. This would move some of the work, and perhaps more of it, off to the applicant to be brought in as prior art information.

An example might be maybe the type of search and parameters that were used, the date of the search, the date of set and the results in a machine readable form and then the examiner can further refine this.

I would also like to point out that the ETO and GCG actually share a large set of customers. And these customers, for example, if you look at the people that have many of the companies that have a high number of patents, such as Tequita, Immunex, Hoffman-LaRoche, Ciba-Giby, ... , Setas, Eli Lilly, those are shared

customers, as well as NIH, University of Washington, University of Texas, New York State University. These are also public institutions that have a high number of patents in this area.

Therefore those people already have many of these tools, and I think that if they don't, there can also be public access to these tools. But there is an incentive to develop new tools that can be supported within this community and these new tools would be in the area of automatic annotation and normalization.

I would also like to state that the strength of the standard tools, which are well supported through GCG software, as well as the strength of Compugen, which supports high throughput solutions, they are working with pharmaceutical companies and addressing many of these issues already with the pharmaceutical companies on how to work with many sequences.

I would also like to add that GCG has a long-term working relationship with public database providers. This is also a key point in that keeping the data up to date and searching against that data so that searches against that data are at the appropriate time, have the appropriate data for when that application is appropriate.

Also GCG has relationships with other software developers and vendors if new algorithms, perhaps in an adjacent area, are also required.

I think that is it.

MR. LEHMAN: Is it your view that apparently we are not using these tools right now that you are describing in our searches and that if we were to do so, we would very substantially reduce these processing times that we are talking about.

MS. SMITH: I think that some of the tools are being used. Like, for instance, the Smith Waterman. It is my understanding that that is being used. It's hard to say what exactly the

tools. The tools I think are interchangeable depending upon the problem that you are searching.

I am making the argument that it's a standard set of tools, that if it can be provided where you can pick and choose the appropriate filter to slip in to the grid that you are creating of filters and not have to go out and look for the new one outside and try to figure how to work that into the solution.

So, I think you have many of the tools already. It's working them into a filtering system and also the machine readable output and normalization.

MR. LEHMAN: So, in theory, if we are using the most efficient filter, the quickest filter, that we would be likely to catch in enough cases a prior art that would invalidate the patent application or the claims that we could just throw that one out and not have to go further.

Is that the point, that it would save us a lot of time?

MS. SMITH: Right. Right.

MR. LEHMAN: The difficulty is though if one assumes that these patent applications will be more and more and more eloquent and won't be able to be thrown off that easily, we will still be stuck with the problem of having to do a more comprehensive search and have finer filters.

MS. SMITH: Right. And it's the ability to slip in those finer filters at an appropriate spot that I think is good about working with standards.

The advantage of the standards is that a large community has tested them and they have kind of been through the mill, so to speak, in that errors have been detected and been fixed and people respect the results.

MR. LEHMAN: Now your company makes the software --

MS. SMITH: Correct.

MR. LEHMAN: -- basically that is used.

I assume the primary purpose of that software isn't really to find the prior art in a patent search, it's to aid in the scientific research itself.

MS. SMITH: Our software is used for many different things, but it's really just basic sequence analysis. So, if you can represent sequences as text, and in the case of DNA you have four nucleotides and proteins, 20 amino acids, that can each be represented by a single letter, our software is basically a large text processor.

So, we are continually adding tools that have been recognized as standards or have come up through much testing, and many of these tools have come from public institutions.

So, it's a solution which you can build around. So, it's a core that will allow you to slip in new tools. In fact, that is what some people do at our customer institutions. They will build new tools on top. Because we don't know what everybody needs. So we try and build a common set based on standards that have been tested and in a sense approved by public opinion and then people build things on top of it because we provide the source code and allow that.

MR. LEHMAN: Any other questions?

MR. KUNIN: I would like to ask -- is this mike on?

MR. LEHMAN: Yes.

MR. KUNIN: The presentation that you made, I didn't quite understand the full impact of what you were saying, seemed to emphasize a substantial amount of front end processing with a discussion of machine readable output.

One of the components that we have indicated here as a significant problem of ours is the post processing. And that is to say that in many instances our problem is not in identifying

hits, but our problem is having very large numbers of hits and then having a very difficult time in using Examiners of having to sort through the outcomes and make the actual patentability determinations.

Do you have any recommendations in terms of taking the machine readable output and doing some post processing that would help take those results and put them in a more orderly way to help the examiner on the back end.

MS. SMITH: I think it would depend upon what level of identity you are willing to accept or not accept.

I am making an assumption that the large number of sequences are due to much ambiguity in an original sequence being allowed, but maybe that is a wrong assumption.

But if there is a lot, if a lot of ambiguity is allowed, then I think it's going to be very hard to attack this.

But if the level of identity that you want can be addressed and put at a certain level, then I think the machine readable output is very good at going through and finding if you attain that level of identity, and then only bringing to the examiner the pertinent information that is at the appropriate level of identity.

MR. LEHMAN: Anybody else?

(No response.)

MR. LEHMAN: If not, thank you very much.

MS. SMITH: Thank you.

MR. LEHMAN: Next I would like to ask Eli Mintz, please, if he is here, to come forward.

MR. MINTZ: Good morning.

My name is Eli Mintz. I am the CO of Compugen and speaking on Compugen's behalf. Compugen manufactures hardware for accelerating sequence searches, homology and similarity

searches. I am also speaking here today on behalf of Silicon Graphics International, SGI, and the points I am going to talk about have received their approval.

I would like to raise four points that I think should help the Patent Office to solve some of its problems. Some of these points are the same as Maggie Smith has raised.

The four points are:

- (1) Cost effective scalable hardware.
- (2) Filtering strategy for searches.
- (3) Automating work flow based on rule based systems.
- (4) Distributed prefiltering at U.S. PTO customer sites.

I would like to speak briefly about each point.

We think that cost effective scalable hardware solution can be built for doing the searching that U.S. PTO requires. A basic building block would cost \$10 per hour and would enable exhaustive searching of 100 sequences each 500 base periods long against a database with sizes one billion base periods in less than 15 hours.

So, relative to the numbers published in the announcement, it's about an improvement of a factor of ten in cost effectiveness.

The chronology that Silicon Graphics has, for example, on how hardware is based on and the GCG software that is used to integrate all this, the technology is all the time evolving and we believe that in the years to come there will be still substantial advancement and the cost of searching will go down.

So, I really don't think that searching will be that much of a problem in the future. I am talking here about the rigorous searches, such as Smith Waterman.

Going back to the filtering strategy, I think it is an important strategy and will bear

fruit say into the future because eventually everything will be prior art. Then the less rigorous searches will quickly fish out results. So it wouldn't make sense to start out with the most rigorous or the more sensitive algorithm right away, but it would be a good idea to prescreen the results, to prescreen the applications, with an algorithm such as Blast that is very quick, not rigorous, but will pick up a lot of homologies.

Let's say in the next few years this may not be the case, but four or five years down the road I am quite confident that most of the filtering will be done at that stage.

The third point, which I think is the one where the U.S. PTO can save a lot is automating the work flow.

Recently there has been some work done by Chris Sanders' group at EBI, the European Bioinformatics Institute, and what they have done, I believe, is a proof of concept of what can be done. Let me just read this out.

The system that they built is called Ginquiz. It is an integrated system for large scale biological sequence analysis that goes from putting sequence to biochemical function using a variety of search and analysis methods and up to date protein and DNA databases.

Applying an expert system module to the results of the different methods, Ginquiz creates a compact summary of findings. It focuses on deriving a predicted put in function based on the available evidence, including the evaluation of a similarity to the closest homologue in the data base, identical, clear, tentative, homoginal.

The analysis used everything that can possibly be extracted from the databases, including three dimensional models by homology when the structure can be reliably calculated.

Ginquiz consists of four modules; the

database update, the search system, the interpretation module and a visualization and browsing system. The models are driven by programs and a front end program for visualization based on a WWW browser is available.

The principal design requirement is the complete automation of all repetitive actions, repetitive subset dates, efficient segment similarity searches, the automated evaluation and interpretation of the results using expert knowledge quoted in rules.

This system has actually been run on a 64 processor Silicon Graphics power challenger ray and it has been used to analyze 6,000 protein sequences from the genome yeast and they plan to analyze the whole yeast genome when it will be available probably later this month.

I think this is a proof of concept. The problem they are trying to solve is more difficult than the problem that the U.S. PTO faces because they want to predict function of a sequence, not just to determine if it is prior art or not. And therefore I think that the technology is available today to allow the U.S. PTO to substantially decrease the Examiner time that it requires and use such automated tools.

The fourth point is, as I said, distributed pre-filtering at U.S. PTO customer sites.

I think the right way to go is to move most of the work to the sites of the people that send in the applications. Because if the U.S. PTO has a defined set of actions that it takes on each application, it would make sense to have the people sending in the applications do this before having sent in the application. And, in my opinion, this can substantially lower the amount of sequences that reach the U.S. PTO, and when they do reach the U.S. PTO, there will already be behind them substantial work done and maybe some of the work

will not have to be repeated.

Especially if, let's say that third parties take the definitions supplied by the U.S. PTO and industry group, it doesn't matter, and build on top of them some software that can be sold or provided to the community, and the U.S. PTO will know that if you use this software, the results are in a format that is acceptable to it, then a lot of the work can be moved from a centralized location towards the people sending in the applications.

That is basically it.

MR. LEHMAN: I take it your assumption is that if we moved this prefiltering out to the applicant site, that they would be able to do it sufficiently rapidly that they would be able to get it into us quickly.

Because, of course, one of the difficulties is if the invention should end up being disclosed in some way, and keep in mind a lot of this research is being done in governmental institutions and some that aren't filing patent applications and maybe publishing the work, that if they are spending a lot of time doing this presearch themselves before they get to us, they would take a risk of having the invention ultimately go into the public domain, certainly in other countries, if not here.

So, would this be able to be done quickly enough, do you think, so that people would not lose an advantage of giving everything they have to the PTO right away?

MR. MINTZ: I believe so. Because the problem that each applicant faces is small relative to the problem that the U.S. PTO faces. Because you have to analyze all the sequences and the applicants have only to analyze their specific sequences. I think this can be a pretty quick process.

Most of the sites that I am aware of can

easily handle just things in house without any problems. They have the capabilities, they have the hardware, they have the software. But they have the building blocks of the software. There needs to be a definition of what exactly should be done with the sequence before sending it into the U.S. PTO.

MR. LEHMAN: Does anybody else have any questions?

(No response.)

MR. LEHMAN: If not, thank you very much.

Did you come all the way from Israel for this?

MR. MINTZ: Yes.

MR. LEHMAN: Next on our list is Hollie Baker.

MS. BAKER: My name is Hollie Baker. I am a senior partner at the law firm of Hale and Dorr in Boston, Massachusetts. I am here on behalf of the American Bar Association, the Intellectual Property Section, where I am Chair of the section's biotechnology committee.

On behalf of the section, I want to thank the Patent Office for having these hearings. We understand how much hard work and time has gone into the hearings, particularly on the reverse side in working with the committee members who have devoted their time and effort in reading the notice and providing some comments to us and preparing our written report which we have submitted to the Patent Office.

We also understand the enormous amount of time that is going to be involved in finding solutions to these issues on nucleotide sequencing.

It wasn't that long ago that I sat in the Patent Office Conference Room with other patent practitioners and with patent examiners where we were first exploring the issue of submitting nucleotide sequences at the first instance. And at

my former law firm, we were one of the test beds for evaluating the patent program.

Technology has moved a long way since that time. Because at the time we were filing patent applications primarily devoted to sequencing of proteins, or perhaps particular sequences with some modifications to make some second generation drugs, vaccines, particular probes for diagnostic uses, and now we are sequencing genomes.

So, just as the technology has moved forward in biotechnology, I think the computer industry has moved forward significantly.

That goes into the first comment that we would like to make.

The Patent Office listed three issues that they wanted to have addressed, and I would like to address the last issue first, which does move into the first issue.

Our section recommends that the Patent Office establish a panel of experts on computer searching to work with the Patent Office to evaluate the Patent Office computer searching and analysis of computer results and to make recommendations for improving the quality and lowering the cost of the searches. With the establishment of this panel, the section believes that it can make the appropriate recommendations for improving the Patent Office search capabilities.

Now, since our committee is not an expert on computers, most of us are patent practitioners and are primarily involved with the patent application evaluation and examination process, we consulted after the April 3rd hearing with a computer company, actually it's a consulting company, who had worked with the SEC, for example, in developing their Edgar program, which you may be familiar with.

This was only to make sure that we were

making appropriate recommendations to the Patent Office in our recommendation that they establish a panel of experts to put together something new for the Patent Office searching capabilities.

Everything that has been mentioned by the previous two speakers was included in a report that they prepared for us, and I have encouraged this company to submit the report as written remarks to the panel. I believe they will be doing that today.

One of the things that was not addressed by the previous two speakers, which was a question by the panel, was: How do you analyze this data once you have prescreened it and once you have prefiltered it? How do you put this together?

This company is not a gene sequencing company. What they really encouraged and were rather appalled by is the amount of data that had to be analyzed in these printouts. They really encourage putting together this information as visual data, as an example, so that perhaps in a graph chart form it can be analyzed in a very particular way.

Apparently this is doable. I don't have the expertise to know how this is done. But this is something that I had not thought of, but certainly is currently capable of being done with the data that is being generated.

In addressing the second issue on underwriting the cost, the section does oppose the imposition of higher fees for patent applications containing a large number of nucleotide and amino acid sequences or long nucleotide or amino acid sequences.

The committee is very aware, the section is very aware as well, that the Patent Office is required under 35 United States Code, Section 41-D, to recover the fees on an estimated average cost of its processing services and materials associated with the patent applications.

While we now know that this hearing is directed to address the problem of a particularly large number of sequences or long sequences, our section based on that makes some recommendations under the nucleotides sequence rules.

Current rules were established that nucleotide submissions had to be made if a biotechnology patent application contained as few as 10 nucleotides or three amino acids, which are 12 nucleotides this requirement applies equally to known prior art sequences, sequences used as probes, sequences used in making constructs, even random sequences that have absolutely no other identifying capability other than their nucleotide sequences.

It also, of course, applies to the claimed invention. And although we are not sure, the Patent Office is obviously more aware of this than we are, we believe it may be contributing to an unwieldy database. We think amendment of the nucleotide sequence rules may eliminate some of the clutter that is in this current database.

The section recommends amending the rules governing the submissions to eliminate the requirement that all nucleotides, amino acid sequences and fragments disclose be submitted and require only those sequences that are claimed to be submitted.

That obviously doesn't get you around the problem that you are having now because apparently all these sequences are being claimed, but it may help the database..

Alternatively, or perhaps additionally, the section recommends amending these rules so that sequence submission will identify new sequences, whether or not those sequences are being claimed, and identify prior art sequences.

If new sequences are then added to claims during prosecution, the applicant could identify

the sequence identification numbers for those sequences and the Examiner could then search those sequences.

This concludes my remarks.

Do you have questions?

MR. LEHMAN: When you said that the rules should be amended to provide that the applicant provide prior art sequences, are you in a sense suggesting that the applicant provide the prior art that we would use to examine the application, that we wouldn't need to go beyond that?

MS. BAKER: Well, most prior art sequences are read already in the public domain somewhere. What we were recommending is that we identify which ones are prior art and perhaps can give a reference as to where those could be located rather than submitting on a computer sequence submission the prior art sequences. Because that is already somewhere in the public domain.

MR. LEHMAN: Thank you very much.

MS. BAKER: Thank you.

MR. LEHMAN: Is Gary Grace here?

MR. PACE: Pace.

MR. LEHMAN: Pace. Sorry. Gary Pace.

MR. PACE: My name is Gary Pace. I am with the Agricultural Biotechnology Research Unit of Ciba Geigy Corporation, which is located in Research Triangle Park, North Carolina.

I come here today as a scientist with 13 years of corporate research experience and 4 years of experience as a patent liaison, including considerable experience with sequence searching. This combination of experience has given me, I think, a reasonable perspective on the problem facing the PTO regarding issues relating to patent protection for nucleic acid sequences.

The PTO is faced with the problem of how to determine obviousness for applications which disclose sequences. Based on the recent demonstrations to the public, it would appear that

a comprehensive structurally based sequence search with extensive reporting of results is being done to examine these cases.

The PTO has predicted that examination of sequences for obviousness would soon swamp the resources of Group 1800, and I submit would also swamp the applicant's ability to underwrite the examination. It is my opinion that this exhaustive approach is not required to adequately examine applications disclosing sequences.

First, I would like to briefly address the established standards for determining obviousness and then, second, apply them to the specific subject of searching sequences.

The Federal Circuit held in, *In re Vaeck*, that a prima facie case of obviousness was established by showing that the prior art, first, suggests making the claimed invention and, second, reveals that a skilled artisan would have a reasonable expectation of success in attaining the claimed invention. I suggest that this standard can be applied to the problem faced by the PTO with regard to sequences.

How would the standard manifest itself in a search strategy? Because of the degeneracy of the genetic code, nucleic acid sequences which bear as little as 70 percent identity, can still encode the same protein.

The Federal Circuit held in the Deuel and Bell cases that a partial or complete protein sequence, combined with a general method of cloning, does not make obvious a specific DNA coding sequence. Therefore, by searching protein names or sequences, then identifying any DNA sequences disclosed therein; one will have ascertained those sequences which are obvious under this standard.

If the applicant's disclosure recites sequences which are different, then the applicant

sequences would be nonobvious under this standard. Hence, for genes of known proteins, at most only a protein search should be sufficient to examine the application.

It should be kept in mind that sequence searching algorithms will always find some similarity between the subject sequence and those present in a database. This creates what one of my colleagues calls meaningless homology.

The key question, however, is what constitutes meaningful homology. I suggest that meaningful homology for the purposes of examination would be those values above which there is a reasonable expectation of success in obtaining the claimed invention.

This means that there should be some rationale basis, other than numerical homology, for concluding that one sequence is obvious in view of another.

If one searched the databases for sequences with meaningful homology, it would mean, for example, that a larger word size could be used in the search algorithm. This would significantly speed up the search and reduce the quantity of search results.

On another point, excessively long sequences often arise from genomic cloning methods. Such sequences, when disclosed, frequently identify open reading frames or ORFs. A straightforward way of searching databases during the examination would be to conduct a search on an ORF by ORF basis rather than by breaking this large sequence up into arbitrary pieces.

In addition, multiple strategies creating an exhaustive search are likely not needed.

First, GenBank is available as a combined source with EMBL, which in turn has incorporated the contents of other databases. The only other database which is reported to be significantly different is GENESEO, which specializes in

sequences disclosed in published applications or issued patents. Hence, for purposes of prior art searching, only at most two databases need be searched.

Second, in the case of GenBank/EMBL the database is broken up into smaller libraries by species, order or some other taxonomic unit. Searching within specific libraries is much less time consuming than searching the entire database.

Third, the choice to search program must be an educated one. For example, it has been reported that one commonly used program will find similarities between sequences even where there is not one single identical residue between them. This would be the stereo typical example of meaningless homology. Without choosing carefully the parameters to use in a search, one obtains reams of output which have limited relevance to the question raised.

Lastly, specialized databases are being developed. For example, a database called DBEST has been created which contains more than 200,000 expressed sequence tags from 26 different organisms. Examination of an application disclosing ESTs might be better accomplished through searching this specialized database.

I would also like to reinforce some of the particular suggestions that have been discussed in the biotechnology industry organization community for the last several weeks regarding sequence listings in general.

First, requiring a sequence to be listed simply because it is disclosed and of a certain length leads to the unnecessary listing of linkers and primers. While these linkers and primers may form part of an enabling disclosure, they are rarely part of the claimed invention. I advocate that only those sequences to be claimed should be required to be part of a formal sequence listing.

Second, it often happens that sequences which are disclosed in a specification are already publicly available. For example, if an applicant has compared their claim sequence to a sequence in the prior art, the sequence rules currently require the prior art sequence also to be listed. This prior art sequence need not be listed since it will not be claimed. Each of these suggestions will reduce the resources needed by the PTO and the applicant to process formal listings.

Lastly, as one who has prepared and repaired many sequence listings, I would like to thank the PTO for distributing their program checker. This program has reduced the frequency of error in our submitted listings, for which we are grateful, since some of our listings have exceeded 50, sometimes reaching 100 pages in length.

To conclude, guidelines and rules are required to define an obviousness standard for sequences and to insure the conduct of informed searches. I believe that the guidance and direction provided by the specification can be turned into an effective search strategy, as is done for key word searches of the prior art. By doing so, the search can be limited to certain criteria based on an understanding of the biology of the claimed invention.

How the claim is drafted should also dictate the search strategy. This approach might require specialized skills, but this is exactly the direction that Group 1800 has taken by hiring examiners with these very skills.

The simplest suggestion that I can make is not to be deceived by an application which discloses sequences. The presence of a sequence, even a claimed sequence, does not necessarily mean that a sequence search is required to adequately determine whether the claimed invention is obvious or not. In many cases the use of gene names, protein names, source organisms, et cetera, can

result in an effective search of the prior art for the purposes of examination. This information can generally be found in the background section of the application.

In addition, most applicants already conduct a search of sequence databases prior to filing. By permitting a submission of sequence searches along the lines of an information disclosure statement, the Examiners may thereby be presented with a useful search strategy and useful search results.

The problems identified by the PTO in regard to these issues require solutions. I submit that some solutions can be achieved quickly and guidelines should be published similar to the approach taken in resolving utility issues.

It should also be realized, however, that biotechnology is one of those areas where technology is outpacing the law. Therefore, it is my belief that these issues will need continual study. Consequently, I suggest that the PTO establish a working group to develop solutions to these problems and to monitor development.

I understand that many offers of assistance have already been made and I wish to add mine to this growing list. This is precisely the type of cooperation needed to address these issues now and in the future.

Thank you.

MR. LEHMAN: Thank you.

Your working group would be presumably outside people, would be industry people, that would be called upon?

MR. PACE: Well, my idea was the working group would be composed of PTO personnel, applicants, scientists, inventors, bioinformatics experts, to work on the problem collaboratively and jointly.

MR. LEHMAN: I am not saying that is not

an excellent suggestion, but there is a potential legal problem. We also heard another recommendation for that. The Federal Advisory Committee Act limits our capacity. There is an overall public policy against not having a million different advisory committees to advise government agencies. We have certain limitations sometimes on our capacity to do that. So we would have to see how that affects these suggestions.

Thank you.

Is there anybody else?

(No response.)

MR. LEHMAN: Thank you very much.

Is Michael Fannon here?

MR. FANNON: Good morning.

My name is Mike Fannon. I am the Director of Bioinformatics at Human Genome Sciences.

As many of you may be aware, HGS is responsible for much of the backlog in terms of these large sequence patents. So I am really pleased to be here to be able to work with you this morning. I have often wondered as we put these things together just how the Patent Office was going to work with these. I am pleased to be able to offer my comments here.

I don't claim to have any expertise in the patent specific issues. However, we have developed substantial expertise in searching and analyzing DNA sequences, and I think much of that can apply in this context.

There are a number of issues associated with searching DNA sequences, and in my work with HGS we, in scaling up our sequencing capacity, really undertook this by a baptism of fire. And there is a number of tradeoffs that you can make in terms of how we actually approach the idea of does the sequence exist in the public domain and how we keep track of use of the sequences.

In particular, I will have some comments

about the sequence search algorithms, the methodology by which we determine whether or not a sequence is similar or related to other sequences, the databases themselves and how we choose what we search against, the organization of the results and the interpretation of the results.

What we find is that you can get reams of output, as we have heard from some of the other speakers, as a result of the searching techniques. We have in our context applied various types of database and user interface techniques to help our scientist wade through those and it may very well be appropriate in this context. And then citation searches, doing some of that in an on line fashion and linking those automatically with the search results.

The issues associated with sequence search algorithms really involve a trade off, and the trade off is pretty simply stated as speed versus sensitivity. That is, the more rigorous the calculation, the longer it is going to take in terms of computational capacity.

When we are looking for searches against prior art, we are really looking for in most cases near identical matches to what is known, in which case many of these techniques can be optimized to search for the near or identical matches, and in this case to reduce the number of these misleading or misinformative matches that you can get by extending these algorithms too far and having them find things that really don't exist or don't have a biological context.

In many cases we found it helpful to combine the algorithms, to use the faster algorithm as a pre-screen to sort through the hundreds of thousands of sequences to create a data set that is much smaller to work with and then to use the more rigorous algorithms to analyze that subset.

So, really in many cases these types of

algorithms tend to be a religious issue in the bioinformatics community. But what we found is the practical solution is to use them, as appropriate, to use the faster algorithms with less sensitivity to do the high speed screening and then to analyze the result set that is the output from that.

Now, the composition of the database you search against is also a very significant issue in any problem that involves large quantities of DNA sequences. Certainly we have all seen in this business the rapid growth of the databases, and, again, HGS has been a very great contributor there as well, in that the technology now enables us to discover sequences at a very high rate.

There is also a well-known redundancy inherent in the public databases and any ability that we can put together to reduce the redundancy of the set that we use as the search set is certainly going to reduce the amount of computational effort required, as well as again helping the Examiners avoid chasing false positives, things that look like hits but really are inappropriate matches of one sort or another.

Another way we could think of subsetting the database for the searches is to organize by date and by species.

In the case of Human Genome Sciences, the bulk of our work is in the human domain, so we tend to analyze our data relative first, initially, against other human sequences and then secondarily against relationships, evolutionary relationships, we may pick up with other species.

So by organizing, the other example that comes to mind is by date. If the application has a certain submission date, if we run that application against the sequences that were known as of that date, then much of the work the Examiner does to determine which came first is in a sense already done.

The matches against newly submitted

sequences won't show up in the listing because they weren't in the database in begin with, and by putting the extra effort into the thinking that goes into what do I search against, we find that, I think, on the back end in terms of Examiner time required to evaluate these matches, that that will go down proportionately.

How the results are organized is an issue that HGS faces on a regular basis as well. We have the capacity to run thousands of sequences in a week and we run these various analytical techniques. The output itself from running these searches now becomes the inputs to our database. That is, we use database management techniques to analyze the search results.

I think much of the state-of-the-art prior to the large sequencing efforts at the Genome centers and from companies like HGS and Insight has been involved in really working on the sequence searching technology. What we are finding is that many of the big shops, such as us, take now the results of those analyses, put them into relational database form. Then we can create listings and create queries that allow the Examiners to really identify those things that are the potential trouble spots, that is, the ones that really are hitting high quality matches to known sequences and the ones that require further evaluation, and to bring those to the foreground very quickly through database management techniques.

Of course, reviewing the search results itself is an extremely time-consuming task. So we would suggest that the Patent Office undertake an initiative to develop some tools for reviewing the database of search results that I am talking about.

This is pretty much standard practice with companies like Insight and HGS, Millenium, the ones that do the large scale sequencing, that their

scientists really don't on the first level interact directly with the search results, but they interact with automatically summarized and catalogued search results using database management techniques.

A logical consistent responsive user interface to that database then would be required to enable the Examiners to make very quick decisions, and in many cases to figure out which ones obviously don't qualify, if we can very quickly go through the set and classify these into groups that identify those things that really are novel, because they don't show sufficient sequence similarity, and just to really, again, help use the computer technology to narrow down the work that the Examiner is required to perform.

A very useful technique that has been explored very much in the public domain by the National Center for Biotech Information is to link the search results with on line databases for citations.

Evaluating results requires a good deal of judgment on the part of the Examiner. What we would envision here is something similar to the Blast searching methodology that is available in the public domain that is sponsored by the National Center for Biotech Information, whereby the results of the search is automatically linked then to GenBank. GenBank is cross-referenced with the midline references to, again, reduce the time, be able to come up with an evaluation of the match in a highly integrated manner without doing a separate sort of literature search. I do believe that the technology is available to really help streamline the problem and I certainly can empathize with the problem you are facing here since we deal with large quantities of DNA sequences and it's very challenging. There is no question about it. The problem domain is very technically demanding and we really applaud your efforts in trying to get a handle on this.

I think, in summary, a combination of techniques is appropriate to streamline the process and I think at every stage of the game, starting from the method that we use to do the searches to what characterizes the database, to how we interact with the search results and make some conclusions, you know, can be developed into an integrated system that would substantially streamline the process as I understand it now.

That is all I have.

MR. LEHMAN: Thank you.

Are there any other questions?

(No response.)

MR. LEHMAN: Thank you very much.

MR. LEHMAN: Is Herb Jervis here?

MR. JERVIS: Good morning.

My name is Herb Jervis. I am the Associate Patent Counsel at SmithKline Beecham Corporation in Philadelphia.

SmithKline Beecham spends about a billion dollars a year on research and development and has an R&D workforce of over 4000 developing new medicines. DNA research is a major platform upon which our discovery programs are built.

In addition to our important alliances with Human Genome Sciences and The Institute for Genomic Research, SB also collaborates with over 140 research institutions and companies involved wholly or partly in DNA research. Meaningful intellectual property protection is fundamental to such an investment.

While other speakers, here today and in San Diego last week, have focused on some of the technical solutions to DNA sequence searching problems cited in the PTO's March 12th Notice and illustrated in the demonstration held on April 3rd, I will confine my remarks to some prosecution-based strategies for easing the searching burden outlined by the PTO.

While the temptation may be present in new areas of technology to search for "quick fixes" to prosecution problems by implementing special rules, such actions I think generally should be resisted because of the isolating effect special regulations and legislations have on the future development of the law with respect to a particular area of technology.

The value of an exceedingly large body of precedent (even if it sometimes appears to be irreconcilable) is that it has resulted from the application of the law to particular facts and has yielded a rich tapestry of illustrations illuminated by accompanying reasoning. It is against this background that the next case can properly be viewed.

It appears from my reading of cases such as Amgen v. Chuagi and Fiers v. Sugano that the Court of Appeals for the Federal Circuit is trying very hard not to treat biotechnological inventions very differently. I think it is fair to characterize the Federal Circuit's view as that DNA is a chemical polymer, albeit a complex one, the rules of chemical practice should apply.

Having made the case against special treatment, I will qualify my remarks and say when viewed rationally and carefully, there should be provisions to assist both the PTO and the applicant in the prosecution of patent applications in certain areas of technology. Certainly, drawing requirements and the rules regarding their representations in mechanical cases and rules concerning the representation of color when it is a distinguishing feature in plant patents illustrate the effectiveness of such an approach.

I have been practicing biotech patent law since the early 1980s and it is from that, dare I say historical, perspective that I wish to cast some more remarks today.

It seems just like yesterday that a young

patent examiner named Jim Martinell (who by the way used to have his name spelled out in genetic code words on his office door) and I struggled with the appropriate language for a declaration to support a deposited microorganism, which would be consistent with the requirements of U.S.C. 112 as we then understood them.

I thank you for indulging me in that bit of reminiscence, but I do so to make a point, and that is the cooperation in this area is key.

The PTO, and Group 1800 in particular, have often cooperated in an open and effective manner with the patent bar in respect of many of these problems surrounding biotech inventions, including the deposit declaration practice referred to, rules governing the representation of nucleic acid sequences. The parties even worked together fostering a legislative initiative (103(b)) thought to be necessary to overcome perceived judicial impediments to biotech process patent. I am not sure the world will forgive us for that.

Biotechnology even has its own section of the MPEP (Chapter 2400). These hearings represent the most recent continuation of that important interaction.

Before making a comment or two about prosecution based strategies, let me make one comment about the technical solutions we have heard today.

I think historically extremely effective interactions relating to biotech prosecution were fostered by the so-called "Group 1800 roundtables" sponsored by the PTO and organizations such as AIPLA, BIO and IPO. It seems to me that the technical aspects of the searching problem would be an ideal topic to be addressed in such a forum.

The success of specialized approaches, notwithstanding, it would be prudent to examine current prosecution practice to see if some

solutions are evident before additional specialized examination regulations are contemplated.

Having said that, let me start by recommending against an approach that has been proffered to simplify searching, and that is a strong reliance on a restriction requirement as a limiting approach. Such an approach I think is fundamentally flawed.

First of all, the problems associated with searching sequences in the context of, for example, the applicants' reliance on functional language, as pointed out in the PTO Notice, does not change if there is a single sequence or a hundred sequences.

Secondly, the over zealous restriction practice is already a subject of much concern within the patent bar. I think further encouragement to utilize restriction to solve these sequencing searching problems would make the problem worse.

In a post-GATT world US inventors are severely disadvantaged by having to file and prosecute large numbers of divisionals, not only in terms of fees, but in terms of ultimate loss of patent term.

I realize some would argue that we are now on the same footing as the rest of the world, except that the rest of the world operates on a much less restrictive unity of invention basis.

Turning to a more positive suggestion, I would like to have the following proposal considered; a two-part examination where non-art issues and art issues are treated separately. I realize that 37 C.F.R. 1.105 and the MPEP Section 707 suggest that office actions be complete and not piecemeal, but I would submit that an office action based on an ineffective search is hardly complete.

If such an approach were to be adopted, issues of utility, enablement of a particular claim scope, adequacy of written description,

definiteness of claim language and the like could be resolved before undertaking the search, thus providing a more focused search inquiry.

I realize that such a suggestion may have the potential for protracting prosecution, but again in a post-GATT world there would seem to be sufficient incentive to resolve such issues quickly.

An efficient 112 dialog between the Examiner and applicant should result in a well-drafted and supported claim of definite scope which will lend themselves to more manageable prior art searching. At the time of the art-based examination, I would envision even greater cooperation between the applicant and the Examiner. It is hard for me to imagine that an applicant would go to the time and expense of filling on a sequence without having done some searching.

Nominally, the results of that search appear as one or more references in an Information Disclosure Statement. If it were helpful to the Examining Corps, why not provide the search itself? I stress if it was helpful because, from my perspective, the most disappointing fact to come out of these discussions so far is that there is not a uniform searching procedure employed.

It would seem to me critical that the PTO, and the patent bar, if appropriate, establish some uniform searching guidelines. If that were so, then some of the search burden may, in fact, be shifted to the applicant.

For example, in the two-part process I have outlined above, should the applicant wish to speed up the prosecution of the search, maybe the search then could be provided by the applicant employing the PTO established protocol. The rules currently in place for making applications special or advancing prosecution would appear to provide a framework for such a process.

Finally, it hasn't escaped my notice that my two-part examination proposal may eliminate one of the Group 1800 Examiners' favorite indoor sports, known in the profession as the old 112/103 squeeze. This feat of intellectual legerdemain occurs when an Examiner seeking to reduce the claim scope alleges that the art to which the invention relates is highly unpredictable, thus the claims must be limited to working examples.

Then in the next paragraph when the Examiner is suggesting that the invention is obviously in view of two tenuously related pieces of prior art, all of a sudden the art to which the invention relates becomes predictable, giving rise to a reasonable likelihood of success.

I won't say this two-part examination process will remove this habit entirely, but separating the grounds of rejection temporally may reduce the temptation.

Thank you for the opportunity of speaking today. I remain ready to assist in resolution of this problem.

MR. LEHMAN: If I understand you right, you are suggesting that by having a two-part examination that we would, first, prior in some cases to doing the search, we would deal with the Section 112 and maybe the Section 101 issues before getting to the search to determine obviousness.

Is that correct?

MR. JERVIS: Yes.

I understood one of the problems is in some of the claim language where the claim recites that all sequences hybridizable therewith, and there is no definition of what that is. It makes a search almost impossible if there is even a single sequence in the application, let alone 100.

MR. LEHMAN: In the software area we recently issued guidelines or we sort of moved in the opposite direction because there was a concern in the industry that we were in effect trying to

get rid of work sometimes by, first, tormenting some of our applicants on 112 and 101 issues. And so we sort of revised our procedures in the form of guidelines -- Nancy can correct me if I am wrong about this -- to more integrate the process. So this would be sort of moving in the other direction.

Would it?

MS. LINCK: We certainly have taken the position that a search should be done prior to the entry of any Section 101 rejections. However, in working with the examining core, it really turns out that the 112 issues do need to be addressed. Although they are not to be entered as a rejection, they need to be addressed prior to conducting this search.

So perhaps maybe the order leading into the application and examining the application would be a compromise between actually having two discreet steps.

I don't know. We hadn't thought about this with respect to the biotech area.

MR. JERVIS: If the 112 issues were resolved first, it may resolve the problem of doing the adequate search in terms of timing and still maintaining a priority date as well because that could be postponed to sometime later.

MS. LINCK: I think we found with the software guidelines that it will be required that the 112 issues be looked into early on.

So, that would be consistent with what Mr. Jervis is suggesting.

MR. JERVIS: Thank you.

MR. KUNIN: You indicated that you opposed restriction requirements. You also seemed to try to draw a line between U.S. restriction practice and, as I believe you characterized it, a more liberal international standard of unity of invention.

But isn't it the case that in applying the international unity of invention standard in places like Japan and the European patent office and elsewhere, that for these types of cases they are holding that the sequences lack the unity of invention?

MR. JERVIS: Well, my personal experience, I haven't actually prosecuted the mega types of sequence cases in the European patent office yet. I have never received in the European patent office a 218 waive restriction requirement, I must say, or unit invention requirement. I have gotten those from the U.S. Patent Office.

What I am saying is that I think it's the application of those rules that needs to be tightened a bit.

But, in general, we file many less divisional applications in Europe than we do in the U.S. as a general rule in biotechnology, not just sequence cases.

MR. LEHMAN: But in this particular category of cases, I think it's our understanding that you would have to file 218 individual patent applications in the European Patent Office.

MR. KUNIN: I believe in the European Patent Office they are making you take them one sequence at a time and saying that each sequence is an independent compound.

MR. JERVIS: Not in my experience they haven't so far.

MR. LEHMAN: Any other questions?

(No response.)

MR. LEHMAN: Thank you very much.

MR. SHPUNTOFF: Thank you.

My name is Albert Shpuntoff. That is S-H-P-U-N-T-O-F-F, being the only name so far that isn't easily spellable from pronunciation.

I work as a consultant very closely with Mass Par. I was formerly the education manager and leader of the post implementation bioinformatics

professional services for Mass Par.

Having listened to the comments here and in La Jolla, I found a lot of commonality with some of the things we have done with customers and felt a need perhaps to avoid having it seem like we were blind sighting the people we have worked with at the patent office as incumbent in the massively parallel processing area with new applications, as one of my colleagues presented at La Jolla.

So, first I would like to respond to a couple of things that were said earlier today.

The wide use of a program does not immediately make it a standard for the industry. There is no standard organization at this point that is saying what hardware or software is standard for this industry. There are a number of competitors who claim a standard at this point is aggressive marketing, which should be seen as such.

I am an admirer of aggressive marketing, but I think one should avoid claiming standards until they truly are standards by an appropriate accrediting organization or industry panel.

I have been involved in implementing a number of automated sequence processing schemes at a number of Mass Par's customers and have been active in advising others who are at the point of starting up an operation.

We have seen quite a variety of strategies for dealing with the overwhelming number of sequences that are to be processed in the discovery phase, as well as is there any point in pursuing it to the Patent Office. So I have seen much of the issues from the other side.

No matter how much processing gets increased, the amount of proposed discovery increases at least as fast. So while we propose ways of working smarter and working harder to obtain results quicker, I think it's fair to say

that the workload does tend to increase as the computing power increases. And as the availability of attractive computing to do bioinformatics in the industry has increased, so certainly has the number of novel results to be presented to the Patent Office.

We have customers who have chosen to do annotation searches on a relational database version of the standard databases to produce a custom version of the database to be searched.

Because it is possible quickly on the Mass Par to produce a searchable database for Smith Waterman searching, we have a number of customers who have chosen to use annotation to restrict the search space and thereby to do more efficient searches, making better use of the parallel time available.

We have a number of sites who have chosen to preprocess databases so as to eliminate potential matches that you have to look at over and over again with different annotations.

There has been a number of mentions of standard software from NCBI that people are recommending be used. One of the products available from them is a product called NRDB, which allows you to take multiple databases and remove identical sequences from additional copies of the database.

There has been a lot of comment at these hearings about the issue of meaningless homology, false hits, large amounts of data coming out of the individual search runs on machines.

We would like to support the idea that many of the false matches are involved with such things as repetitive DNA elements, which are parts of sequences that are to be submitted, such things as aloe repeats.

There are databases of just the aloe repeats which might well be an additional very useful augmentation to the search to help to

identify in perhaps an automated fashion what are the meaningless homology hits during the search process.

In setting up high throughput screening for several pharmaceutical companies this has been sufficiently important to make the operation practical that we have made it the second step in an automated processing. After identifying that the sequence being looked at is of sufficient quality to even proceed with analysis, the next step has been to mask out repetitive DNA and aloe sequences with the idea of providing more high quality hits and reducing the number of false hits that have to be followed through by an Examiner.

So, this has been an important part, I believe, in the La Jolla hearings. The gentleman from Insight spoke about this also being part of their automated sequence processing.

To the degree that the Patent Examiners are spending too much time following hits based on repetitive sequences not key to the art, but which show up as statistical artifacts, it is possible to develop a process which involves masking those prior to running searches.

MR. LEHMAN: Does that have to be done like on an individual basis, each time you have to sort of program?

You call it annotation. Do you have to annotate the program for the particular search that you are doing so that the Examiner would have to become proficient in that search technology or is that something you could standardize?

MR. SHPUNTOFF: Where we have done this and had it contribute, we have used a database which is available at NCBI called the rep base, which is a database of repetitive DNA elements. It is possible to run a relatively simple search. Even Fass Day or Blast are sufficient to identify these repetitive sequences. You don't particularly

care to have the most sensitive search for things that are going to be masked out.

But even if it's just to run an additional search of these to aid the examiner as a general what in this sequence is in the aloe base or repetitive DNA base already to aid in not following with additional searches, those things which are relatively unlikely to be of significance.

In the case that we have automated we actually make this a formal first step and some small percentage of the sequences being searched are almost immediately ruled out as being completely aloes. But for the most part this allows for the output of the first round of searches to be of higher significance by eliminating the most common matches.

Another focus of the work we have been doing has been to post process the outputs of MP search. As we have heard, there is a lot of interest in what can be done in terms of post processing.

Frequently our customers have been taking the outputs and putting them into either relational databases for maintaining sequence databases or feeding them back into lab management systems based on standard database systems.

We are able to parse the reports that are produced using the statistics that are an output of the Smith Waterman technique to provide keys to what further searches might be done, and in a number of the lab settings have been able to choose, based on whether or not we have high matches of a particular sort early during the process, to automatically generate additional searches which are appropriate based on the kind of match that occurred at the beginning.

So, in some settings this has led to the equivalent of a family of paradigm searches which Examiners might use through something like the

existing graphic interface to deal with sort of standard searches based on particular paradigms where requests fall within particular sets of parameters.

I think I will stop with that.

MR. LEHMAN: Thank you.

Steve.

MR. KUNIN: Could you comment on the suggestion that was made in San Diego by the representative from Mass Par with respect to the clustering technique?

There was an indication that perhaps a number of the sequences had a fairly high degree of similarity that they could be clustered together and perhaps treated as a batch.

Do you have any additional comments along those lines.

MR. SHPUNTOFF: I think that what John Burke was talking about is very current research that is being used throughout the community. There will be a number of conferences in which various clustering techniques will be talked about in the very near future with the idea of improving the way with which we do searches.

The databases at present contain much redundancy, many attempts to sequence things, which have resulted in what should be identified as a cluster and for which there could be a consensus gene representation generated through techniques such as clustering and multiple sequence alignment.

The database that was mentioned earlier today, DBEST, is an attempt to try to provide a cleaner database for expressed sequence tags with the attempt being to do the sort of clustering analysis and multiple sequence alignment prior to presenting the database to be searched.

Whether the processing is done within the Patent Office to maintain an indexed and smaller

database, whether the clustering technique is used to help understand the commonality in sequences being provided by an applicant, we feel it's a useful technique which has been parallelized for the machine and one which should be integrated into the processes.

The discussion earlier about word base search and the possibility of using longer word size in doing searches that would be a little bit faster would be relevant to the particular software he was discussing and PT-2 cluster which was developed at the University of Houston and of which he is one of the authors.

MR. LEHMAN: Thank you very much.

Has Michael Langan arrived yet?

(No response.)

MR. LEHMAN: If not, that concludes the witnesses who I have signed up.

Has anyone else signed or is there anyone else who would like to testify at this time?

(No response.)

MR. LEHMAN: If not, that concludes our hearing.

Let me mention that the written comments on the notice of hearings and request for public comment must be submitted by today, I guess, by the end of business today. And a transcript of this hearing will be made available as soon as we can make it available, as well as all the written comments that we have received, and that will be available for inspection and review on or about May 13, 1996 in Room 520 of Crystal Park 1. That is at 2011 Crystal Drive. And it will be available also on the Internet at ftp.uspto.gov. Ftp.uspto.gov.

All written comments and oral comments made here today will be taken into consideration before we implement any policy on this issue. We can't promise though that any comments received after today will be taken into consideration.

I would like to remind those present

today that the next public hearing will be held on May 2nd, from 9:00 a.m. to 5:00 p.m. in this room on issues related to patent protection for therapeutic and diagnostic methods. And notice for comments and public hearing on that issue was published in the March 13, 1996 Federal Register, 61 Federal Register 10320 and also in the Official Gazette, 1185 OG 64.

That concludes the hearing today. I would like to thank all the witnesses that came for their help and all the interested parties that came to hear what they had to say.

Thank you.

(Whereupon, at 10:40 a.m. the proceedings adjourned.)